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CONTENTS

JULY

EDITORIAL: Personal reflections 1
G. Smith

CLINICAL INVESTIGATIONS

Ropivacaine 0.75% for extradural anaesthesia in elective Caessarean section: an open clinical and pharmaco-kinetic study in mother and neonate.... 3
C. P. J. Morton, S. Bloomfield, A. Magnusson, H. Jozwiak and J. H. McClure

Serum concentrations of bupivacaine during prolonged continuous paravertebral infusion in young infants 9
S. L. W. Cheung, P. D. Booker, R. Franks and M. Pozzi

Gut mucosal perfusion in infants undergoing cardiopulmonary bypass: effect of preoperative captopril 14
P. D. Booker, A. J. M. Davis and R. Franks

Interactions between mivacurium and pancuronium 19
K. S. Kim, J. C. Shim and D. W. Kim

Blood flow and mivacurium-induced neuromuscular block at the orbicularis oculi and adductor pollicis muscles.. 24
M. Abdulatif and M. El-Sanabary

Comparison of extradural and general anaesthesia on the fibrinolytic response to total knee arthroplasty 29
N. E. Sharrock, G. Go, P. Williams-Russo, S. B. Haas and P. C. Harpel

Cardioventilatory coupling during anaesthesia......... 35
D. C. Galletly and P. D. Larsen

Effect of domperidone on the ventilatory response to transient hyperoxia in patients anaesthetized with isoflurane........ 41
I. T. Foo, P. M. Wsarren and G. B. Drummond

Accuracy and clinical performance of a continuous intra-arterial blood-gas monitoring system during thoracoscopic surgery..... 47
A. Zollinger, D. R. Spahn, T. Singer, M. P. Zalunardo, S. Stoehr, W. Weder and T. Pasch

Midlatency auditory evoked potentials and motor signs of wakefulness during anaesthesia with midazolam 53
D. Schwender, M. Daunderer, N. Schnatmann, S. Klasing, Ul. Finsterer and K. Peter

Intradermal compared with prick testing in the diagnosis of anaesthetic allergy........ 59
M. McD Fisher and C. J. Bowey

Plasma dilution and the rate of infusion of Ringer's solution 64
R. G. Hahn and C. Svensén

LABORATORY INVESTIGATIONS

R22290

Beneficial effect of concomitant administration of isoflurane and nicorandil........ 68
V. Piriou, S. Ross, D. Pigott, R. Evans and P. Foex

Effect of halothane on K^+ and carbachol stimulated [^{3}H]noradrenaline release and increased [Ca^{2+}]$_i$ in SH-SY5Y human neuroblastoma cells........ 78
R. Archeson, K. Bjornstrom, R. A. Hirst, D. J. Rowbotham and D. G. Lambert

Role of endothelium in the modulation of isoflurane-induced vasodilatation in rat thoracic aorta.......... 84
P. Kirstetter, F. Lagneau, O. Lucas, V. Krupa and J. Marty

Halothane reduces reperfusion injury after regional ischaemia in the rabbit heart *in vivo*........ 88
W. Schlack, B. Preckel, H. Barthel, D. Obal and V. Thämer

Effects of alfentanil on cerebral haemodynamics in an experimental model of traumatic brain injury...... 97
M. J. Souter, P. J. D. Andrews, I. R. Piper and J. D. Miller

Quantitative study of Lowe's square-root-of-time method of closed-system anaesthesia........ 103
J. M. Couto da Silva, W. W. Mapleson and M. D. Vickers

REVIEW ARTICLE

Thoracoscopic sympathectomy in the treatment of palmar hyperhidrosis: anaesthetic implications.... 113
B. Fredman, D. Olsfanger and R. Jedeikin

SHORT COMMUNICATIONS

Extradural buprenorphine suppresses breast feeding after Caesarean section........ 120
M. Hirose, T. Hosokawa and Y. Tanaka

Administration of magnesium sulphate before rocuronium: effects on speed of onset and duration of neuromuscular block........ 122
B. Kussman, G. Shorten, J. Uppington and M. E. Comunale

Dystrophin deficient *mdx* muscle is not prone to MH susceptibility: an *in vitro* study........ 125
N. Mader, H. Gilly and R. E. Bittner

Effects of ketamine and pentobarbitone on acetylcholine release from the rat frontal cortex *in vivo* 128
T. Kikuchi, Y. Wang, H. Shinbori, K. Sato and F. Okumura

ABSTRACTS

Proceedings of the Anaesthetic Research Society, Leicester Meeting, March 20–21, 1997........ 131P

CORRESPONDENCE

Absence of memory for intraoperative information.. 143
Sevoflurane or halothane for paediatric endoscopy .. 143
Spinal anaesthesia: effect of the site of injection on the spread of analgesia........ 144
Cuff deflation for easier weaning from ventilation... 145
Prophylaxis against deep vein thrombosis 145
Intraocular pressure and suxamethonium 146

BOOK REVIEWS

Handbook of Critical Care, 2nd Edn........ 147
Practical Obstetric Anaesthesia........ 147
Cambridge Textbook of Accident and Emergency Medicine........ 147

AUGUST

EDITORIAL: Resuscitation........ 149
P. J. F. Baskett and L. Strunin

RESUSCITATION

Basic life support........ 151
A. J. Handley

Management of the airway and ventilation during resuscitation ... 159
D. A. Gabbott and P. J. F. Baskett

Advanced life support guidelines ... 172
C. E. Robertson

Paediatric and neonatal life support ... 178
D. A. Zideman

Drugs in modern resuscitation ... 188
R. Vincent

Peri-arrest arrhythmias ... 198
D. Chamberlain

Fibrillation and defibrillation of the heart ... 203
L. L. Bossaert

Immersion, near-drowning and drowning ... 214
F. St C. Golden, M. J. Tipton and R. C. Scott

Aspects of resuscitation in trauma ... 226
J. P. Nolan and M. J. A. Parr

Uniform reporting in resuscitation ... 241
W. F. Dick

Ethical aspects of resuscitation ... 253
M. Mohr and D. Kettler

CORRESPONDENCE

Oxygenation criteria – a plea for more information ... 260
Lateral positioning for regional analgesia during labour ... 260
Interactions between mivacurium and prilocaine ... 262
Effects of volume on spinal anaesthesia with 0.25% hyperbaric bupivacaine ... 262
Converting pH and H^+ ... 262
"Renal" dopamine ... 263

BOOK REVIEWS

Manual of Drug Interactions for Anaesthesiology, 3rd Edn ... 265
Critical Care, 3rd Edn ... 265
Pain Management for the Practising Physician ... 265
The Pulmonary Circulation: Moving From Passive to Active Control ... 266
The Pulmonary Artery Catheter in Critical Care – A Concise Handbook ... 266
Hyperthermic and Hypermetabolic Disorders ... 266
Intensive Care Manual, 4th Edn ... 266
Critical Care Medicine: Perioperative Management ... 267
Stabilisation and Transport of the Critically Ill ... 267

Errata ... 268

SEPTEMBER

EDITORIALS:

I So just who was James "Young" Simpson? ... 271
S. M. Rae and J. A. W. Wildsmith

II Propofol in paediatric intensive care ... 274
D. J. Hatch

CLINICAL INVESTIGATIONS

Metabolic, biochemical and haemodynamic effects of infusion of propofol for long-term sedation of children undergoing intensive care ... 276
P. H. Martin, B. V. S. Murthy and A. J. Petros

Comparison of sevoflurane and halothane for outpatient dental anaesthesia in children ... 280
S. T. Paris, M. Cafferkey, M. Tarling, P. Hancock, P. M. Yate and P. J Flynn

Comparison between halothane and sevoflurane for adult vital capacity induction ... 285
J. E. Hall, T. A. Oldham, J. I. M. Stewart and M. Harmer

Laryngeal mask airway and uncuffed tracheal tubes are equally effective for low flow or closed system anaesthesia in children ... 289
D. Frohlich, B. Schwall, W. Funk and J. Hobbhahn

Caudal tramadol for postoperative analgesia in paediatric hypospadias surgery ... 293
D. P. Prosser, A. Davis, P. D. Booker and A. Murray

Comparison of single, end-holed and multi-orifice extradural catheters when used for continuous infusion of local anaesthetic during labour ... 297
M. A. S. Dickson, C. Moores and J. H. McClure

Transient neurological symptoms afer spinal anaesthesia with 4% mepivacaine and 0.5% bupivacaine ... 301
A. Hiller and P. H. Rosenberg

Comparison of volume controlled with pressure controlled ventilation during one-lung anaesthesia ... 306
M. Tuğrul, E. Çamcı, H. Karadeniz, M. Şenturk, K. Pembeci and K. Akpir

Acute effect of mitral valve replacement on extravascular lung water in patients receiving colloid or crystalloid priming of cardiopulmonary bypass ... 311
W. Buhre, A. Hoeft, B. Schorn, A. Weyland, M. Scholz and H. Sonntag

Acute normovolaemic haemodilution decreases postoperative allogeneic blood transfusion after total knee replacement ... 317
D. Olsfanger, B. Fredman, B. Goldstein, A. Shapiro and R. Jedeikin

Ondansetron compared with metoclopramide in the treatment of established postoperative nausea and vomiting ... 322
P. Diemunsch, C. Conseiller, N. Clyti, J. P. Mamet and the French Ondansetron Study Group

Histological support for the difference between malignant hyperthermia susceptible (MHS), equivocal (MHE) and negative (MHN) muscle biopsies ... 327
P. Mezin, J.-F. Payen, J.-L. Bosson, E. Brambilla and P. Stieglitz

Detection of a novel mutation at amino acid position 614 in the ryanodine receptor in malignant hyperthermia ... 332
K. A. Quane, H. Ording, K. E. Keating, B. M. Manning, R. Heine, D. Bendixen, K. Berg, R. Krivosic-Horber, F. Lehmann-Horn, T. Fagerlund and T. V. McCarthy

Changes in inflammatory mediators during orthotopic liver transplantation ... 338
M. C. Bellamy, H. F. Galley and N. R. Webster

Environmental monitoring during gaseous induction with sevoflurane ... 342
J. E. Hall, K. A. Henderson, T. A. Oldham, S. Pugh and M. Harmer

LABORATORY INVESTIGATIONS

Effect of haemoglobin concentration on brain oxygenation in focal stroke: a mathematical modelling study ... 346
F. Dexter and B. J. Hindman

Actions of tramadol, its enantiomers and principal metabolite, O-desmethyltramadol, on serotonin (5-HT) efflux and uptake in the rat dorsal raphe nucleus ... 352
T. A. Bamigbade, C. Davidson, R. M. Langford and J. A. Stamford

Dopamine and intestinal mucosal tissue oxygenation in a porcine model of haemorrhage ... 357
R. Germann, M. Haisjackl, B. Schwarz, N. Salak, E. Deusch, W. Pajk, H. J. Wolf, B. Riedmann and W. Hasibeder

Effects of magnesium sulphate on the cardiovascular

system, coronary circulation and mycocardial metabolism in anaesthetized dogs 363
Y. Nakaigawa, S. Akazawa, R. Shimizu, R. Ishii, S. Ikeno, S. Inoue and R. Yamato

REVIEW ARTICLE

Pain after laparoscopy 369
J. I. Alexander

SHORT COMMUNICATIONS

Twitch augmentation and train-of-four fade during onset of neuromuscular block after subclinical doses of suxamethonium 379
S Y. Kim, J. S. Lee, S. C. Kim and W. Park

Spontaneous movements associated with rocuronium: is pain on injection the cause? 382
A. Borgeat and D. Kwiatkowski

Rapid tracheal intubation with propofol, alfentanil and a standard dose of vecuronium 384
R. Groener and D. G. Moyes

Haemolysis after etomidate: comparison of propylene glycol and lipid formulations 386
A. Doenicke, M. F. Roizen, R. Hoernecke, M Mayer, P. Ostwald and J. Foss

Enhanced choline acetyltransferase activity does not explain the action of inhaled convulsants 389
R. Griffiths, P. Ionescu, Z. Fang, D. D. Koblin and E. I. Eger

CASE REPORTS

Sevoflurane for difficult tracheal intubation..... 392
S. M. Mostafa and A. M. J. Atherton

Transient radicular irritation after spinal anaesthesia with 2% isobaric lignocaine. 394
D. Ramasamy and R. Eadie

Unsuspected difficult intubation caused by a laryngeal web 396
Z.-K. Chong, B. Jawan, Y.-Y. Poon and J.-H. Lee

EQUIPMENT

Laboratory evaluation of the 1-NOvent nitric oxide delivery device... 398
J. D. Young, M. Roberts and L. B. Gale

COMMENTARY

Clinical evidence for delayed chloroform poisoning 402

CORRESPONDENCE

Converting pH and H$^+$: a rule for the other thumb 410
MAC values of mixtures.................. 410
The expanding role of simulators in risk management 411

BOOK REVIEWS

Clinical Anaesthesia 412
Textbook of Neuroanesthesia with Neurosurgical and Neuroscience Perspectives........ 412
Anesthesia and Perioperative Care of the Combat Casualty 412
Thrombopoiesis and Thrombopoietins· Molecular, Cellular, Preclinical and Clinical Biology 413

Erratum 413

OCTOBER

EDITORIALS:

I Postoperative respiratory dysfunction: is the site of surgery crucial?..................................... 415
H. McKeague and A. J. Cunningham

II ORG 21465, a new water-soluble steroid hypnotic: more of the same or something different? 417
J. W. Sear

III Meta-analysis: greater than the sum of its parts? 417
M. J. Souter and D. F. Signorini

CLINICAL INVESTIGATIONS

Postoperative spirometry after laparoscopy for lower abdominal or upper abdominal surgical procedures 422
J. Joris, A. Kaba and M. Lamy

Administration to humans of ORG 21465, a water soluble steroid i.v. anaesthetic agent.................... 427
J. R. Sneyd, P. M. C. Wright, M. Cross, P. Thompson, G. Voortman, M. M. Weideman, C. J. H. Andrews and C. J. Daniell

Computer-controlled infusion of ORG 21465, a water soluble steroid i.v. anaesthetic agent, into human volunteers 433
J. R. Sneyd, P. M. C. Wright, D. Harris, P. A. Taylor, P. C. M. Vijn, M. Cross, H. Dale, G. Voortman and P. Boen

Prognosis of intraoperative brachial plexus injury: a review of 22 cases 440
B. Ben-David and S. Stahl

Does the addition of clonidine affect duration of analgesia of bupivacaine wound infiltration in inguinal hernia surgery?.......... 446
S. Elliott, S. Eckersall, L. Fligelstone and S. Jothilingam

Comparison of suxamethonium and different combinations of rocuronium and mivacurium for rapid tracheal intubation in children........................... 450
M. Naguib, A. H. Samarkandi, A. Ammar and A. Turkistani

Effect of temperature and cardiopulmonary bypass on the pharmacokinetics of remifentanil 456
D. Russell, D. Royston, P. H. Rees, S. K. Gupta and G. N. C. Kenny

Influence of pulse oximeter lower alarm limit on the incidence of hypoxaemia in the recovery room.... 460
A. T. Rheineck-Leyssius and C. J. Kalkman

Does nitrous oxide antagonize sevoflurane-induced hypnosis?.................................. 465
T. Katoh, K. Ikeda and H. Bito

Effect of incremental doses of sevoflurane on cerebral pressure autoregulation in humans 469
S. Gupta, K. Heath and B. F. Matta

Comparison of isoflurane with propofol on respiratory cilia ....:.... 473
J. H. Raphael and M. W. Butt

Platelet function is inhibited by nitric oxide liberation during nitroglycerin-induced hypotension anaesthesia.. 476
H. Aioki, M. Inou, T. Mizobe, M. Harada, H. Imai and A. Kobayashi

Validity of acoustic quantification colour kinesis for detection of left ventricular regional wall motion abnormalities: a transoesophageal echocardiographic study 482
T. Hartmann, N. Kolev, A. Blacher, C. Spiss and M. Zimpfer

LABORATORY INVESTIGATIONS

Repeated enflurane anaesthetics and model predictions: a study of the variability in the predictive performance measures 488
P. M. Vermeulen, J. G. C. Lerou, R. Dirksen, L. H. D. J. Booij and G. F. Borm

A physiological model of induction of anaesthesia with propofol in sheep. 1. Structure and estimation of variables 497
R. N. Upton and G. L. Ludbrook

A physiological model of induction of anaesthesia with propofol in sheep. 2. Model analysis and implications for dose requirements 505
G. L. Ludbrook and R. N. Upton

Overestimation of low cardiac output measured by thermodilution 514
J. P. Tournadre, D. Chassard and R. Muchada

Effect of temperature on the solubility of desflurane, sevoflurane, enflurane and halothane in blood 517
G. G. Lockwood, S. M. Sapsed-Byrne and M. A. Smith

Studies on the binding of $[^3H]$amethocaine to rat cerebrocortical membranes 521
T. Kudo, M. Kudo, K. Hirota and D. G. Lambert

Dissociation between the effect of nitrous oxide on spontaneous and reflexly evoked sympathetic activity in dogs 525
D. Ma, C. Wang, C. K. Pac-Soo, M. K. Chakrabarti and J. G. Whitwam

REVIEW ARTICLE

Anaesthesia for the surgery of emphysema 530
I. D. Conacher

SHORT COMMUNICATIONS

Granisetron reduces the incidence of nausea and vomiting after middle ear surgery 539
Y. Fujii, H Toyooka and H. Tanaka

Comparison between alfentanil, pethidine and placebo in the treatment of post-anaesthetic shivering 541
I. J. Wrench, G. Cavill, J. E. H. Ward and A. W. A. Crossley

CASE REPORT

Thermal softening of tracheal tubes: an unrecognized hazard of the Bair Hugger active patient warming system 543
J. L. Ayala and A. Coe

CORRESPONDENCE

Low-dose dopamine· there is a scientific rationale... 546
External cooling in critically ill febrile ICU patients 546
Inhaled nitric oxide 547
Predominant involvement of motor fibres in patients with critical illness polyneuropathy 547

BOOK REVIEWS

Applied Cardiovascular Physiology (Update in Intensive Care and Emergency Medicine Series) 549
Principles and Practice of Pharmacology for Anaesthetists, 3rd Edn 549

NOVEMBER

EDITORIALS: I "Walking extradurals" in labour: a step forward? 551
C. D. Elton, P. Ali and M. C. Mushambi
II Anaesthesia and the competence revolution 555
J. D. Greaves

CLINICAL INVESTIGATIONS

Pharmacokinetic and clinical study of ropivacaine and bupivacaine in women receiving extradural analgesia in labour 558
A. F. McCrae, P. Westerling and J. H. McClure

Magnetic resonance imaging of the extradural space of the thoracic spine 563
Y. Hirabayashi, K. Saitoh, H. Fukuda, T Igarashi, R. Shimizu and N. Seo

Pharmacokinetic–pharmacodynamic modelling of the EEG effects of Ro 48-6791, a new short-acting benzodiazepine, in young and elderly subjects 567
J. Dingemanse, J. Haussler, W. Hering, H. Ihmsen, S. Albrecht, M. Zell, H. Schwilden and J. Schuttler

Pharmacokinetics of midazolam given as an intranasal spray to adult surgical patients 575
S. Bjorkman, G. Rigemar and J. Idvall

Magnetic resonance spectroscopy of isoflurane kinetics in humans. Part I: elimination from the head 581
G. G. Lockwood, D. P. Dob, D. J. Bryant, J. A. Wilson, J. Sargentoni, S. M. Sapsed-Byrne, D. N. F. Harris and D. K Menon

Magnetic resonance spectroscopy of isoflurane kinetics in humans. Part II: functional localization... 586
G. G. Lockwood, D. P. Dob, D. J. Bryant, J A. Wilson, J. Sargentoni, S. M. Sapsed-Byrne, D. N. F. Harris and D. K. Menon

Differential effects of nitrous oxide and propofol on myogenic transcranial motor evoked responses during sufentanil anaesthesia 590
L. H. Ubags, C. R. Kalkman, H. D. Been and J. C. Drummond

Emergence times from xenon anaesthesia are independent of the duration of anaesthesia 595
T. Goto, H. Saito, Y. Nakata, S. Uezono, F. Ichinose and S. Morita

Effect of systemic N-methyl-D-aspartate receptor antagonist (dextromethorphan) on primary and secondary hyperalgesia in humans 600
S. Ilkjær, J. Dirks, J. Brennum, M. Wernberg and J. B. Dahl

Comparison of perioperative ketoprofen 2.0 mg kg^{-1} with 0.5 mg kg^{-1} i.v. in small children during adenoidectomy 606
E. Nikanne, H. Kokki and K. Tuovinen

Knee–chest *vs* horizontal side position during induction of spinal anaesthesia in patients undergoing lumbar disc surgery 609
E. Laakso, M. Pitkanen, J. Kytta and P. H Rosenberg

Pharmacokinetics of vecuronium during acute isovolaemic haemodilution 612
F. S. Xue, X. Liao, S. Y. Tong, J H. Liu, L. Li, Q. Zou and L. K. Luo

LABORATORY INVESTIGATIONS

Effects of volatile anaesthetics on spontaneous action potential firing of cerebellar Purkinje cells *in vitro* do not follow the Meyer–Overton rule 617
B. Antkowiak, H. Hentschke and K. Kirschfeld

Comparison of the effects of isoflurane with those of propofol on pulmonary vascular impedance in experimental embolic pulmonary hypertension 625
P. Ewalenko, S. Brimioulle, M. Delcroix, P. Lejeune and R. Naeije

Extra-pulmonary effects of inhaled nitric oxide in swine with and without phenylephrine 631
E. Troncy, M. Francœur, I. Salazkin, F. Yang, M. Charbonneau, G. Leclerc, P. Vinay and G. Blaise

Reduction in nitrogen dioxide concentration by soda lime preparations during simulated nitric oxide inhalation 641
J Weimann, J. U. Hagenah and J Motsch

REVIEW ARTICLE

Catalogue of human error 645
F. Arnstein

SHORT COMMUNICATIONS

Pre-emptive analgesia using local anaesthesia: a study in bilaterally symmetrical surgery 657
W. I. Campbell and R. W. Kendrick

Intra-articular morphine and clonidine produce comparable analgesia but the combination is not more effective 660
M. Gentili, P. Houssel, M. Osman, D. Henel, A. Juhel and F. Bonnet

Autotransfusion in major orthopaedic surgery: experience with 1785 patients 662
B. Borghi, E. Pignotti, M. Montebugnoli, A. Bassi, M. Corbascio, N. de Simone, K. Elmar, U Righi, A. M. Laguardia, S. Bugamelli, F. Cataldi, R. Ranocchi, M. A. Feoli, T. Bombardini, G. Gargioni, A. G. Franchini and G. C. Caroli

Continuous intra-arterial blood-gas monitoring in infants and children with cyanotic heart disease.. 665
M Hatherill, S. M. Tibby, A. Durward, V. Rajah and I. A. Murdoch

CASE REPORTS

Extradural catheter-related infections in patients with infected cutaneous wounds 668
M. Bengtsson, H. Nettelblad and F. Sjoberg

A case of cardiac hydatidosis 671
S. Laglera, M. A. Garcia-Enguita, F. Martinez-Gutierrez, J. P. Ortega, A. Gutierrez-Rodriguez and A. Urieta

ABSTRACTS

Proceedings of the Anaesthetic Research Society, Bristol Meeting, July 3–4, 1997 .... 674P

CORRESPONDENCE

Thorascopic sympathectomy................................. 688
Simulated anaesthetic emergencies.... 689
Pigs are not humans 691
Obstruction of the lumen of a plastic 15-mm connector inserted into a cut paediatric tube—Is it possible to avoid this damage? 692

BOOK REVIEWS

Positioning in Anesthesia and Surgery, 3rd Edn........ 693
1997 Yearbook of Intensive Care and Emergency Medicine 693

DECEMBER

EDITORIALS.

I Inhaled nitric oxide in acute respiratory failure 695
J. D. Young
II "Ecstasy" and the anaesthetist 697
A. P. Hall

CLINICAL INVESTIGATIONS

The intubating laryngeal mask. I: development of a new device for intubation of the trachea 699
A. I. J. Brain, C. Verghese, E. V. Addy and A. Kapila

The intubating laryngeal mask. II: a preliminary clinical report of a new means of intubating the trachea 704
A. I. J. Brain, C. Verghese, E. V. Addy, A. Kapila and J. Brimacombe

The intubating laryngeal mask airway: an initial assessment of performance 710
A. Kapila, E. V. Addy, C. Verghese and A. I. J. Brain

Skin vasomotor reflex induced by laryngoscopy: comparison of the McCoy and Macintosh blades. 714
O. Shimoda, Y. Ikuta, S. Isayama, M. Sakamoto and H. Terasaki

Effect of felodipine on renal function and vasoactive hormones in infrarenal aortic surgery 719
L. de Lasson, H. E. Hansen, B. Juhl, W. P. Paaske and E. B. Pedersen

Effects of temperature on phrenic nerve and diaphragmatic function during cardiac surgery......... 726
G. H. Mills, Z. P. Khan, J. Moxham, J. Desai, A. Forsyth and J. Ponte

Changes in regulators of the circulation in patients undergoing lung surgery 733
J. Boldt, M. Papsdorf, D. Uphus, M. Müller and G. Hempelmann

I.v. fentanyl decreases the clearance of midazolam .. 740
I. Hase, Y. Oda, K. Tanaka, K. Mizutani, T. Nakamoto and A. Asada

Pharmacodynamics of thiopentone: nocifensive reflex threshold changes correlate with hippocampal electroencephalography 744
D. P. Archer and S. H. Roth

Effect of extradural analgesia on paradoxical arousal response of the electroencephalogram 750
S. Kiyama and J. Takeda

Time-frequency spectral analysis of heart rate variability during induction of general anaesthesia 754
H.-H. Huang, H.-L. Chan, P.-L. Lin, C.-P. Wu and C.-H. Huang

Assessment of a new ventricular contractile index obtained with transoesophageal echocardiography before and after cardiopulmonary bypass in cardiac surgical patients 759
M Kikura, T. Ikeda, T. Ohnuma and K. Ikeda

Heat retention using passive systems during anaesthesia: comparison of two plastic wraps, one with reflective properties.................................... 766
S. Deacock and A. Holdcroft

Comparison of the accuracy of the lithium dilution technique with the thermodilution technique for the measurement of cardiac output 770
T. Kurita, K. Morita, S. Kato, M. Kikura, M. Horie and K. Ikeda

Detection of arrhythmogenic cellular magnesium depletion in hip surgery patients 776
G. Zuccalà, M. Pahor, F. Lattanzio, S. Vagnoni, F. Rodolà, P. De Sole, A. Cittadini, A. Cocchi and R. Bernabei

Partly exhausted soda lime or soda lime with water added, inhibits the increase in compound A concentration in the circle system during low-flow sevoflurane anaesthesia...................................... 782
G. Moriwaki, H. Bito and K. Ikeda

REVIEW ARTICLE

Opioid systems and the newborn 787
D. F. Marsh, D. J. Hatch and M. Fitzgerald

SHORT COMMUNICATIONS

Prevention of hypothermia by cutaneous warming with new electric blankets during abdominal surgery 796
Y. Camus, E. Delva, A. E. Bossard, M. Chandon and A. Lienhart

Hypnotic effect of i.v. thiopentone is enhanced by i.m. administration of either lignocaine or bupivacaine 798
M. Tverskoy, I. Ben-Shlomo, M. Vainshtein, S. Zohar and G. Fleyshman

Effect of methohexitone and propofol with or without alfentanil on seizure duration and recovery in electroconvulsive therapy 801
T. T. Nguyen, A. K. Chhibber, S. J. Lustik, J. W. Kolano, P. J. Dillon and L. B. Guttmacher

Pharmacokinetics of controlled release morphine (MST) in patients with liver cirrhosis 804
H. I. M. Kotb, M. Y. El-Kabsh, S. E. S. Emara and E. A. Fouad

CASE REPORTS

Subclavian aneurysm causing brachial plexus injury after removal of a subclavian catheter 807
F. M. Walden

Anaesthesia for laparoscopic cholecystectomy in a patient with Eisenmenger's syndrome................. 810
M. S. Sammut and M. L. Paes

CORRESPONDENCE

Ropivacaine test dose in extradural anaesthesia 813
Use of inhaled nitric oxide in the critically ill 813
Management of the airway and ventilation during resuscitation.......... 814
Weaning: is the work of breathing via a tracheostomy tube similar to that via a tracheal tube?.......... ... 814
Continuous intra-arterial blood-gas monitoring....... 815
The future of ethical treatment.......... 817

BOOK REVIEWS

Practical Anaesthesia and Analgesia for Day Surgery 818
MCQs and OSCEs for the Primary FRCA 818
Methods in Molecular Biology, volume 83: Receptor Signal Transduction Protocols........ 818
Essentials of Pediatric Intensive Care, 2nd Edn 818
Manual of Acute Pain Management in Children 819
Anesthesia and Resuscitation 819
Cardiac Anaesthesia: A Practical Handbook 819
Anaesthetic Physiology and Pharmacology 820
Rapid Sequence Review of Anaesthesiology with Time-limited Pressure 820

Index to Volume 79 821

Papers for publication and all editorial communications should be addressed to:
Dr J. M. Hunter,
Editor-in-Chief, *British Journal of Anaesthesia*,
University Department of Anaesthesia,
Royal Liverpool University Hospital,
The Duncan Building,
Daulby Street,
Liverpool L69 3GA.
Tel./Fax: 0151 706 4005

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EDITORIAL

Personal reflections

July 1997 marks the completion of my 10-yr term of office as Editor of the *British Journal of Anaesthesia*. Prior to 1987 I acted for 5 yr as the Editor of Educational Issues and was responsible for producing two issues of the Journal per year (normally January and July) devoted to review articles grouped into a single theme. In common with Dr Saidman, commenting in his final editorial on retirement from the editorship of *Anesthesiology*,[1] I also can state that these 15 yr have been one of the most enjoyable periods of my professional life, largely because of liaison with a diverse range of interesting and talented individuals, both scientists and clinicians, working in fields which extend beyond the boundaries of anaesthesia into basic sciences, community medicine and clinical laboratory disciplines. Furthermore, I have had the opportunity of collaborating with professional editors, publishers and experts in the printing industry. The insight, interest and opportunities provided by these contacts have compensated for the heavy workload of editing the Journal and being tied to the inexorable demands of monthly schedules.

In 1987, the *British Journal of Anaesthesia* published some 10 general issues per year and two postgraduate educational issues. The flow of manuscripts was such that each general issue contained of the order of 15–17 manuscripts per issue. There was a relatively long acceptance to publication interval and despite a modest submission rate of manuscripts, a full-time secretary was necessary as all material was processed manually in paper format. In 1987 my initial desire was to try to improve the interest for our readers by incorporating into every issue editorials, review articles, original articles, book reviews and correspondence. My intention in improving service to authors was to attempt to deal with all correspondence as expeditiously as possible, obtain rapid peer review assessments of high quality and achieve as low an acceptance to publication interval as possible.

With the manual system of handling all correspondence, improvements in many of these areas could be achieved only by computerization, and in 1991 a computerized database was installed in the office of the *British Journal of Anaesthesia*. This resulted in a dramatic improvement in the speed at which material could be processed and consequently, over the past 10 yr, the acceptance to publication interval for our Journal has diminished to almost 4 months; at the same time there has been a three-fold increase in the rate of submission of manuscripts to the Journal. Every issue since 1987 has carried at least one or two editorials. By reducing the number of postgraduate issues to one per year, it was thought that this would permit a free-standing review article to appear in each issue of the Journal, but this has not always been achieved.

An irritating trend over the past 10 yr has been the publication of several abstracting journals in which summaries of papers from the main peer-reviewed journals have been published together with a brief synopsis of the views of individuals. While this is acceptable competition in the free market economy, we would challenge the assertion of the supporters of these endeavours that it removes the necessity to read the original peer-reviewed articles. Brief overviews of original articles reflect the views of the individual composing that review and often such descriptions require interpretation in the light of any bias possessed by the reviewer, particularly when accompanied by a brief and personalized bibliography. The short synopsis should not however, be confused with the large review article (which has undergone peer review) published in this and other scientific journals where there is extensive referencing and a clear attempt to place all literature in a specific field into the appropriate perspective, often with the origination of new hypotheses.

The past 10 yr has also seen increased competition for the *British Journal of Anaesthesia* from the formation of other peer-reviewed specialist anaesthetic journals and the growth in size of the other general major anaesthetic journals. Despite these challenges, we have continued to attract high quality papers for publication; the *British Journal of Anaesthesia* has also grown in size and consequently we are now publishing of the order of 25 manuscripts per issue, almost double that in 1987, and our rejection rate has increased from approximately 45% to 60%.

There have been other major changes in the *British Journal of Anaesthesia* over the past 10 yr. In January 1990 the *BJA* became the official journal of the College of Anaesthetists and subsequently in 1992 the journal of the Royal College of Anaesthetists (RCA).[2] At the same time, in 1992, the Journal changed to the A4 format. Of the manuscripts submitted to the *BJA* in 1992, 40% originated from the UK, 29% from the remainder of Europe and 30% from the rest of the world. Between 1992 and 1996 there was a 20% increase in the number of manuscripts submitted, as a result of a 13% increase from Europe, 11% increase from the remainder of the world but a 4% decrease from the UK, despite our link with the RCA. To date, of the manuscripts accepted for publication from those submitted in 1996, 31% originated from the UK, 34% from elsewhere in Europe and 35% from the remainder of the world. The decrease in submission of articles from the UK provides evidence, I believe, of the severe problems in the UK affecting academic anaesthesia which I described in a recent editorial.[3]

This progressive and extensive change from a journal publishing material originating from the UK to one publishing predominantly from outside the UK has been accompanied by a broadening of the geographical origins of the membership of our editorial board, and the forging of collaborative links with *Anesthesia and Analgesia*, our US sister journal which was founded 1 yr before the *British Journal of Anaesthesia* and is currently celebrating its 75th anniversary.

Other major innovations in which the *BJA* has been involved include the development of the TEAL project. This CD-ROM incorporating 5 yr of articles from the four leading anaesthetic journals in the world has unquestionably been an outstanding success and annual meetings of all four editors-in-chief will continue to maintain the momentum in improving and extending this service to the benefit of our readers.

Although computerization of our database handling system has enabled the Journal to grow without an increase in secretarial input, the same is not true of the editorial arrangements. Until 1997, the Journal was managed largely by an editor with the assistance of two associate editors. However, commencing in July 1997 the new Editor-in-Chief, Dr Jennifer Hunter, will be assisted by a panel of four section editors, who will look after specific sub-specialties in anaesthesia.

Because of the long interval between submission of manuscripts and publication and the 4-month interval between acceptance and publication, there will be a change-over period during which both Dr Hunter and myself will act as Editors-in-Chief from July 1997 to January 1998 and thereafter my involvement will cease. It should be noted that from June 1997, all new manuscripts and new letters to the editor should be sent to Dr Hunter.

The task of editing the *BJA* would be impossible without the support and advice of the editorial board and assistance from a large panel of manuscript reviewers. These individuals, who are inevitably busy and committed professionals, fulfil a demanding task; perhaps only an editor can truly appreciate the dedication and effort involved.

Despite this aid, the new Editor-in-Chief will continue to face problems in producing a high quality scientific journal. It seems inevitable but unfortunate that there will continue to be a growth in the number of journals, both subscription and sponsored, and also an increase in the number of articles being presented to the *BJA* for possible publication, although as noted elsewhere by Greene,[4] this will not necessarily be accompanied by a parallel improvement in quality. However, I have no doubt that while it may not be possible to detect an improvement in scientific quality within a period of a few years, quinquennial comparisons reveal a steady and continuous improvement in the scientific quality of what is published in the *BJA*. Furthermore, I have been delighted by the improvement in the standard of English composition in articles accepted for publication from countries where the native language is not English, although this does not apply to many that are rejected. This change has been so great since 1987 that the extent of subediting required now differs little from that required for manuscripts emanating from the UK and North America. I am grateful to all authors for preferring the *BJA* to other journals and for their work in meeting our requirements for submission of manuscripts

It is important that the increase in workload for our Journal does not place too great an imposition on individual assessors, which is a problem as the increase in specialization of manuscripts renders it difficult to maintain a large panel of assessors with the necessary degree of expertise in the appropriate area. In addition, while there has not, to our knowledge, been any documented case of fraudulent material published in the *British Journal of Anaesthesia*, recent events in other specialist journals suggest that increased vigilance is necessary on the part of both the editorial team and assessors to safeguard against this problem. I am confident that the new editorial team will respond to all of these challenges and that the *BJA* will continue to retain its place among the leading journals of anaesthesia.

G. SMITH
Editor

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British Journal of Anaesthesia 1997; 79: 3–8

CLINICAL INVESTIGATIONS

Ropivacaine 0.75% for extradural anaesthesia in elective Caesarean section: an open clinical and pharmacokinetic study in mother and neonate

C. P. J. Morton, S. Bloomfield, A. Magnusson, H. Jozwiak and J. H. McClure

Summary

In an open study we have investigated the efficacy of 20 ml of 0.75% ropivacaine (7.5 mg ml^{-1}) to provide extradural anaesthesia for elective Caesarean section. Plasma concentrations (total and free) were estimated in the mother and neonate. Anaesthesia was effective and safe. Plasma concentrations of ropivacaine in the mother and neonate were within safe limits and consistent with previous studies. Two mothers received accidental i.v. injections of ropivacaine 75 mg and 150 mg, respectively, without serious adverse effects. (*Br. J. Anaesth.* 1997; **79**: 3–8).

Key words
Anaesthesia, obstetric. Anaesthetic techniques, extradural. Anaesthetics local, ropivacaine. Pharmacokinetics, ropivacaine

Ropivacaine (1-propyl-2', 6' pipecoloxylidide hydrochloride monohydrate) is a new, long-acting, amide-type local anaesthetic which has a chemical structure similar to that of bupivacaine, the butyl group being replaced by a propyl group. It differs also in that it is prepared as the pure S isomer rather than as a racemic mixture. *In vivo* animal studies have suggested that central administration of both drugs produces similar patterns of onset and extent of sensory and motor block, but that ropivacaine has a shorter duration of action[1] and causes less motor block.[2] In humans, extradural administration of ropivacaine produces sensory block similar to that produced by the same volume and concentration of bupivacaine, but motor block is slower in onset, shorter in duration and less intense.[3] In addition, ropivacaine at similar plasma concentrations is less cardiotoxic in both animals[4] and humans.[5]

The advantages of extradural, rather than general, anaesthesia for mother[6] and baby[7] for Caesarean section are well documented. However, onset time is relatively slow, block may sometimes be patchy, asymmetrical or limited in extent, and visceral pain may be experienced by up to 50% of patients.[8] Bupivacaine 0.75% has been said to approach the ideal for a single agent for extradural anaesthesia for Caesarean section[9] but fears of toxicity led to withdrawal of its approval for use in obstetrics. An agent of similar potency to, but less toxicity than, 0.75% bupivacaine could be a useful alternative to the drugs currently available for extradural anaesthesia for Caesarean section.

The objectives of this study were to investigate the efficacy of 0.75% ropivacaine 20 ml to provide extradural anaesthesia for Caesarean section, to determine the effect of this dose of ropivacaine on the neonate, to measure the maximum total plasma concentration of ropivacaine in the mother, and total and free concentrations of ropivacaine in umbilical and maternal veins at delivery. An open design was chosen because 0.75% ropivacaine had not been used before in obstetric anaesthesia.

Patients and methods

Thirty-eight women (ASA I and II) carrying a full term ($\geq$37 weeks) singleton fetus undergoing elective Caesarean section under extradural anaesthesia gave informed consent to the study which was approved by the hospital Ethics Committee. Women with diabetes, placenta praevia, pregnancy-induced hypertension or carrying a baby judged small for dates were excluded, as were those with a history of substance or alcohol abuse. Other reasons for exclusion were height less than 152 cm or weight more than 100 kg.

Premedication comprised ranitidine 150 mg the night before and 2 h before operation. On arrival in the anaesthetic room maternal heart rate and arterial pressure were recorded, a cardiotocograph attached and 30 ml of sodium citrate 0.3 mol $litre^{-1}$ given orally. Hartmann's solution 1 litre was administered i.v. while the extradural catheter was inserted and the block established.

After infiltration of the skin with lignocaine, a 16-gauge Tuohy needle was inserted into the extradural space via the first or second lumbar interspace using a midline approach and loss of resistance to saline. A lateral eyed extradural catheter was inserted 3–4 cm in a cephalad direction, the catheter taped in place

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C. P J. Morton, FRCA, J. H. McClure, BSC, FRCA (Department of Anaesthetics); S. Bloomfield, MD, MRCP (Department of Neonatal Paediatrics), Royal Infirmary of Edinburgh NHS Trust, Lauriston Place, Edinburgh EH3 9YW. A Magnusson, MSC, H Jozwiak, BA, Astra Pain Control AB, Sodertalje, Sweden
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and the mother turned to the wedged supine position. Provided that neither blood nor CSF were obtained on aspiration, 0.75% ropivacaine 3 ml were injected as a test dose. Five minutes after the end of the test dose, in the absence of signs of intravascular or intrathecal injection, 0.75% ropivacaine 17 ml were injected incrementally over 2 min.

Loss of sensation to pinprick (27-gauge short-bevel needle) was assessed at 5-min intervals for 30 min, and at 45 min and 60 min. At 60 min only the upper sensory level was assessed because surgery had already started. Motor block was assessed, at the same times, according to a modified Bromage scale (0=no motor block, 1=inability to raise extended leg (just able to move knee), 2=inability to flex knee (able to move foot only), 3=inability to flex ankle joint (unable to move foot or knee)). Surgery was not started unless there was bilateral loss of sensation to pinprick from T6 to S3; if this had not been achieved at 45 min, 5-ml increments of 2% lignocaine with adrenaline 1 in 200 000 were given and the patient withdrawn from further efficacy assessments. After operation sensory levels and motor block were assessed at 30-min intervals until return of normal sensation and motor power.

Pain on skin incision, quality of analgesia, as judged by the patient and anaesthetist, and quality of neuromuscular block, as judged by the obstetrician, were recorded. Times from skin incision to uterine incision, and uterine incision to delivery, and whether or not the uterus was exteriorized were noted.

Maternal heart rate and arterial pressure were measured at 3-min intervals from the end of the test dose until the end of surgery. Fetal heart rate was measured continuously until the start of surgery. After surgery maternal heart rate, arterial pressure, upper and lower sensory levels and motor power were measured at 30-min intervals until the block had regressed.

Evaluation of the newborn was performed by Apgar score at 1 and 5 min after birth and by neurological and adaptive capacity score (NACS)[10] at 2 h and 24 h after delivery.

Adverse events occurring from the start of anaesthesia to discharge from hospital, either observed by attending staff or reported by the patient in response to standard questions, were recorded. Apart from treatment of pain during extradural block, which was specified in the design, decisions on management of adverse events were made by the appropriate clinical staff. A telephone call enquiring after the mother and baby was made 2–3 weeks after discharge.

Maternal blood samples were obtained from a peripheral vein immediately before administration of the test dose, at the end of extradural injection, at 10-min intervals for 60 min and at delivery. A sample of umbilical venous blood was obtained after the cord was clamped. Samples of maternal and umbilical venous blood were obtained at delivery and pH was measured immediately on the labour ward (Instrumentation Laboratories); all other blood samples were centrifuged at 3000 rpm for 10 min, the plasma withdrawn and then frozen. Samples were analysed at the end of the study by the Department of Bioanalysis, Astra Pain Control AB, Södertälje, Sweden. Total concentrations of ropivacaine were measured using gas chromatography with a nitrogen sensitive detector[11] and free concentrations were measured by coupled column liquid chromatography after ultrafiltration of the plasma samples.[12] For total concentrations the limit of quantification was set at 0.008 mg litre^{-1} and interassay precision was 2.5–5.7% in the concentration range 0.027–1.141 mg litre^{-1}. For free concentrations the limit of quantification was set at 0.003 mg litre^{-1} and interassay precision was 2.1–8.4% at a concentration of 0.026 mg litre^{-1}. Recovery was close to 100% for both assays. Alpha$_1$-acid glycoprotein (AAG) concentrations were measured by a radioimmunodiffusion procedure.[13]

The following measurements were made: (1) maternal samples: total ropivacaine concentration immediately before the test dose, at the end of extradural injection, at 10-min intervals for 60 min and at delivery; free ropivacaine concentration immediately before the test dose, at 20 min and at delivery; AAG concentration immediately before the test dose, and at delivery; and (2) umbilical vein samples: total and free ropivacaine concentration and AAG concentration.

Results

Seven patients were excluded from efficacy analysis because of technical failure or study violation (including two patients who received accidental i.v. injections of ropivacaine). In addition, one patient with poor venous access declined to have an i.v. cannula sited for blood sampling and samples for one patient were not frozen. Therefore, results from 31 patients were valid for analysis of efficacy and 29 for pharmacokinetic analysis. All patients who received ropivacaine were followed-up with respect to safety. The characteristics of the 31 patients included in the study are shown in table 1.

Table 1 Patient characteristics (31 patients) (mean (SD) [range])

Age (yr)	29.8 [23–44]
Height (cm)	162 (6.0) [152–173]
Weight (kg)	72.5 (8.9) [54–91]

SENSORY BLOCK

Twenty-six of the 31 patients (84%) had a sensory block to pinprick from T6 to S3 (which was defined as adequate for surgery) at 45 min. Four patients required increments of 2% lignocaine with adrenaline 1 in 200 000 to achieve adequate block; one of these had surgery delayed because the obstetric staff were required urgently elsewhere and eventually underwent Caesarean section under subarachnoid block. These four patients, together with one patient who did not develop a block below L4, were not included in the analysis of duration of motor and sensory block. Times to onset and duration of sensory block at various dermatomes are shown in table 2.

Table 2 Times to onset (min) and duration (h) of sensory and motor block (31 patients)

	Onset			Duration		
	Median	Quartiles	Range	Median	Quartiles	Range
Sensory block						
S3	23	15, 28	13–40	4.1	3.1, 5.9	2.0–7.7
S1	20	13, 28	5–45	4.4	3.5, 6.0	1.8–7.6
L5	15	13, 23	5–45	4.5	3.3, 5.5	2.1–7.6
L3	10	8, 15	5–25	4.3	3.4, 5.4	2.4–7.1
L1	5	5, 10	5–13	4.3	4.0, 5.3	1.9–7.1
T12	8	5, 10	5–13	4.4	4.1, 5.3	1.9–6.6
T10	10	8, 15	5–38	4.4	3.9, 4.7	2.8–6.5
T8	13	10, 15	5–35	3.7	3.3, 4.6	1.8–6.0
T6	15	13, 20	5–38	3.4	2.6, 3.9	1.3–5.8
Motor block						
Grade I	18	13, 25	6–45	2.2	1.8, 3.1	1.3–5.1
Grade II	26	20, 30	11–45	1.7	1.5, 3.4	1.3–4.2
Grade III	25	25, 38	20–45	1.6	1.4, 2.5	1.1–3.7

MOTOR BLOCK

Of the 31 patients who were eligible for efficacy assessment, grade I motor block developed in 30 (97%) patients, grade II in 16 (52%) and grade III in 11 (35%), at 45 min. Times to onset and duration are shown in table 2. Sensory block outlasted motor block by a median time of 2 h 30 min (range 1 h 15 min to 5 h 30 min).

SURGERY

Duration of the different stages of anaesthesia and surgery are shown in table 3. Although many patients had a block adequate for surgery within 25 min (table 2) the study design did not permit surgery to start until 45 min after the start of extradural injection. In addition, further delay sometimes occurred because the operating theatre was in use.

No patient reported pain on skin incision. The quality of anaesthesia was judged as excellent or good by the patient and satisfactory by the anaesthetist in 25 of the 26 patients (96%) who were eligible for efficacy assessment, although 10 patients (39%) reported vague symptoms suggestive of incomplete visceral block. In one case quality of anaesthesia was judged to be poor by the patient and unsatisfactory by the anaesthetist. This patient, who had an adequate somatic block, reported severe visceral pain and required i.v. morphine when her uterus was exteriorized for suturing. Quality of abdominal wall muscle relaxation was judged adequate by the obstetrician in all 26 patients.

CARDIOVASCULAR EFFECTS

There was a mean decrease in maternal systolic and diastolic arterial pressures of 15% from baseline in the first 30 min; maternal heart rate was stable. Treatment of hypotension was left to the discretion of the anaesthetist; 25 of 31 patients were treated with ephedrine. Fetal heart rate was stable in all but three babies. In two of these fetal bradycardia was associated with maternal hypotension and both reverted to a satisfactory rate when the mothers were turned on their left side and hypotension was corrected. In the third, an unexplained fetal tachycardia resolved spontaneously after 3 min without specific action being taken.

NEONATAL ASSESSMENTS

Umbilical vein pH was normal (7.25–7.5) in all but one baby. In this case umbilical vein pH was 7.1 and concurrent maternal vein pH was 7.29; repeat measurement of maternal vein blood revealed a pH of 7.45. The baby was vigorous at birth with Apgar scores of 7 and 10, therefore the low values were attributed to machine measurement error. The pH of maternal vein blood was normal (7.35–7.45) in all but three other mothers in whom the abnormality was slight (pH 7.32–7.34).

Thirty neonates had an Apgar score of 7 or more at 1 min and all had a score of 9 or 10 at 5 min. NACS at 2 and 24 h are shown in table 4.

ACCIDENTAL I.V. INJECTION OF ROPIVACAINE

Two patients received accidental i.v. injections of ropivacaine. In both cases the test dose of 22.5 mg (3 ml) of ropivacaine had been uneventful. The first patient received another 7 ml of 0.75% ropivacaine before developing unequivocal symptoms of i.v. local anaesthetic. The injection was stopped, the extradural catheter resited and another 3+17 ml of 0.75% ropivacaine injected. Blood samples were

Table 3 Times (min) of surgical events relative to the end of the main dose (31 patients)

	Median	Quartiles	Range
End of injection–skin incision	56	52, 61	43–114
Skin incision–uterine incision	7.5	6, 11	2–22
Skin incision–delivery	10	7, 12	3–23
Duration of surgery	40.5	32, 49.5	11–60

Table 4 Neurological and adaptive capacity scores (NACS) (No. of neonates)

		NACS									
Time	*n*	30	31	32	33	34	35	36	37	38	39
2 h	31	2	3	3	6	7	5	2	1	2	0
24 h	31	0	0	2	0	2	5	8	7	5	2

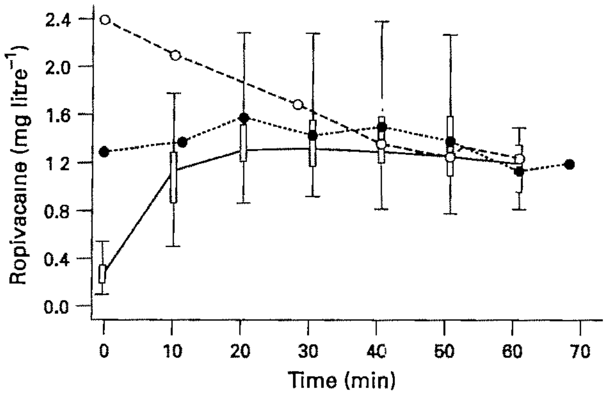

Figure 1 Total plasma concentration of ropivacaine after administration of ropivacaine 150 mg i.v. (○) and extradural ropivacaine 150 mg administered 28 min after ropivacaine 75 mg i.v. (●). For comparison, the data from the patients (n=28) who received extradural ropivacaine 150 mg are shown by the box and whisker plot. Median values are connected; box is first and third quartiles, whiskers are maximum and minimum values.

obtained after the end of the second 17-ml extradural injection and at 10-min intervals thereafter. The second patient received approximately the same dose of ropivacaine before developing symptoms mildly suggestive of i.v. injection. The symptoms resolved quickly when the injection was stopped, and did not recur until the entire 20 ml of 0.75% ropivacaine had been injected. Blood samples were obtained as soon as the extradural injection had finished and at 10-min intervals thereafter. Plasma concentrations in these two patients, compared with plasma concentrations in patients who received uneventful extradural anaesthesia are shown in figure 1.

MISCELLANEOUS EVENTS

One baby was considered to have transient tachypnoea of the newborn. One baby had a small midline gum defect and one required surgery for pyloric stenosis some weeks after discharge. One baby was reluctant to breast feed for 4 days but fed satisfactorily when bottle feeding was started. One baby was reported to vomit after feeds throughout the study. When followed-up 6 weeks after discharge, he was still vomiting occasionally but gaining weight.

In the period between leaving the recovery room and discharge from hospital, one mother reported backache and two reported leg pain. No mother complained of residual effects of extradural anaesthesia or the technique at follow-up by telephone 2–3 weeks after delivery.

PHARMACOKINETICS

In addition to the nine patients excluded from pharmacokinetic analysis, five individual blood samples from four other patients were excluded because of handling errors. Valid results were available from 29 patients (table 5). Mean maximum maternal ropivacaine concentration ($C_p$max) was 1.47 (SD 0.28) mg litre^{-1}, occurring at a mean time (tC_pmax) of 40 (13) min after extradural injection. At the time of delivery, mean umbilical vein concentrations were: total 0.37 (SD 0.18) mg litre^{-1}; free 0.06 (0.015) mg litre^{-1}. Mean umbilical vein/maternal vein (UV/MV) ratios for total and free concentrations were 31 (17) % and 74 (16) %, respectively. Mean free fraction (fu) in the neonates (0.18 (0.06)) was greater than in mothers (0.07 (0.02)).

Table 5 Maximum total concentration of ropivacaine ($C_p$max), time to $C_p$max (tC_pmax, total (C) and free (Cu) concentrations of ropivacaine, and alpha$_1$ acid glycoprotein (AAG) concentrations in maternal and umbilical (UV) veins at specified times (n=9)

	Mean	SD	Range
$C_p$max (mg litre^{-1})	1.47	0.28	0.94–2.39
tC_pmax (min)	40	13	17–63
Before anaesthesia			
AAG (μmol litre^{-1})	13	4	6–28
At 20 min			
C (mg litre^{-1})	1.36	0.28	0.86–2.28
Cu (mg litre^{-1})	0.10	0.03	0.05–0.16
fu	0.08	0.02	0.04–0.13
At delivery			
C (mg litre^{-1})	1.25	0.32	0.78–2.39
Cu (mg litre^{-1})	0.09	0.04	0.05–0.23
fu	0.07	0.02	0.03–0.11
C (UV) (mg litre^{-1})	0.37	0.18	0.20–1.12
Cu (UV) (mg litre^{-1})	0.06	0.02	0.04–0.09
fu (UV)	0.18	0.06	0.06–0.29
C (UV)/ C	0.31	0.17	0.12–0.84
Cu (UV)/ Cu	0.74	0.16	0.32–1.06
AAG (μmol litre^{-1})	12	3	7–22
AAG (UV) (μmol litre^{-1})	5	2	3–14

Discussion

The open design of this study prevents a true comparison of ropivacaine with other agents for extradural anaesthesia in Caesarean section. The majority (84%) of our patients had a block adequate for surgery after extradural administration of 20 ml of 0.75% ropivacaine. Twenty-five of these patients (96%) assessed their anaesthesia as good or excellent. All patients had neuromuscular block that was adequate for surgery. Noble and others,[14] in a study from the same centre, assessing adjuncts to extradural bupivacaine for Caesarean section, reported that 37 of 42 (88%) patients had a block adequate for surgery after 20 ml of 0.45% bupivacaine (with adrenaline 5 μg ml^{-1}, fentanyl 100 μg, or both) and 83% rated analgesia as good or excellent. However, 49% of their patients required supplementation during surgery, compared with one of 26 in our study.

Norton, Davis and Spicer[15] compared 16–20 ml of 0.5% bupivacaine with 2% lignocaine with adrenaline; 25% of patients required supplementary local anaesthetic to achieve bilateral block to T6. The procedure was pain free in only 53% of patients and 12% reported discomfort that was distressing. In a large retrospective clinical review, Crawford, Davies and Lewis[16] reported that approximately 12% of patients undergoing Caesarean section under extradural anaesthesia required some form of supplementation to their original block.

It was notable that we found marked separation between the offset of motor and sensory block. Theoretically this should provide analgesia for some hours after return of motor function but in some patients sensation returned in the area of the surgical incision at a relatively early stage. Comparison of motor block with that reported in other studies is difficult because of the potential for observer variation.

The cardiovascular effects were those expected of extensive extradural block in mothers at full term.

Umbilical vein pH, used as a measure of adequate placental perfusion, was normal in all but one case, in whom maternal venous pH was also decreased. These results were not consistent with the clinical condition of either the mother or baby and as repeat measurement of maternal venous pH was normal, the results were considered to be spurious. Only two babies had an unsatisfactory Apgar score at 1 min; both improved rapidly after oxygen therapy. All babies had satisfactory Apgar scores at 5 min.

The neurological and adaptive capacity scoring (NACS) system[10] was devised as a scoring test to differentiate between the more generalized neurological depression associated with drugs and anaesthesia, and that associated with asphyxia or birth trauma in term infants (≥37 weeks). A score of 35 or greater indicates a neurologically vigorous neonate. In our study, 20 of 30 babies at 2 h and four of 31 at 24 h had a score of less than 35. However, there was no control group for comparison.

Ropivacaine 0.5% has been compared with 0.5% bupivacaine for extradural anaesthesia for elective Caesarean section.[17] There were no differences between the two drugs in terms of cardiovascular effects or profile of sensory block. Time of onset and intensity of motor block were the same but duration of motor block was less with ropivacaine. There was no difference in neonatal outcome as assessed by Apgar score, umbilical cord blood-gas tensions or NACS at 2 and 24 h.

One baby in our study was admitted to the special care baby unit suffering from transient tachypnoea of the newborn. This baby's mother had received a higher dose of ropivacaine than intended (225 mg, of which 75 mg was given i.v.). Transient tachypnoea of the newborn is attributed to delay in resorption of fetal lung fluid after delivery and is characterized by tachypnoea and increased oxygen requirements. The incidence after delivery by elective Caesarean section is approximately 9%. The chest wall is not subject to the forces experienced in vaginal delivery and thoracic gas volume is less. Most infants recover in 2–3 days, as was the case in this neonate and there were no long-term sequelae. Neither transient tachypnoea of the newborn nor the other miscellaneous events were thought to be related to ropivacaine.

With the exception of the two women who received accidental i.v. injections there were no maternal symptoms attributable to central nervous system (CNS) local anaesthetic toxicity. Scott and colleagues[5] reported early mild symptoms of CNS toxicity at venous plasma concentrations of ropivacaine of 1–2 mg litre^{-1}. However, the subjects in that study received i.v. infusions of ropivacaine 10 mg min^{-1} and symptoms occurred within 15 min of the start of infusion. In an earlier study the same author[18] reported that toxicity occurred at lower peak plasma concentrations during rapid, compared with slow, infusion of local anaesthetic. The rate of increase and absolute value of plasma concentration was considered to influence the development of toxicity.

The test dose of 3 ml of 0.75% ropivacaine in our study failed to predict intravascular catheter placement on the two occasions that accidental i.v. injection occurred. On these occasions symptoms of i.v. local anaesthetic did not occur until another 7 ml of 0.75% ropivacaine (52.5 mg) had been injected. In one patient the symptoms were so equivocal that the injection was restarted when her symptoms resolved and it was not until the injection was completed that symptoms returned. This patient, who received a total of 150 mg of ropivacaine i.v. had no obvious effects other than failure to develop a block.

The time to maximum plasma concentration and its variability in this study were almost identical to those in a previous study[19] of the same dose of extradural ropivacaine in non pregnant patients but the $C_P$max value in our study was greater and more widely distributed. This is consistent with a study in sheep[20] which demonstrated slower clearance of ropivacaine during pregnancy.

Local anaesthetics are small molecules which, when unionized, are lipid soluble. The unbound, free portion crosses the placenta readily, and at equilibrium the free concentration is the same in the mother and neonate.[21 22] In the fetal circulation equilibrium occurs between the bound and unbound local anaesthetic. Plasma concentration of AAG, to which ropivacaine is bound extensively, is less in the neonate than in the mother, therefore total plasma concentration of ropivacaine is less in the neonate than in the mother, but the free fraction is greater.

In our study mean $C_P$max occurred before delivery and therefore maternal plasma ropivacaine concentration was declining at the time of delivery. At this time Cu (UV) was less than Cu (maternal vein), implying that equilibrium between maternal and fetal circulations had not been achieved.

In summary, 20 ml of 0.75% ropivacaine provided safe and effective extradural anaesthesia for Caesarean section. The commonest side effect was hypotension, consistent with extradural block. Two patients tolerated accidental i.v. injection of ropivacaine (75 mg and 150 mg, respectively), reporting only early symptoms of toxicity. There were no other adverse events attributable to systemic local anaesthetic toxicity. Maternal and umbilical vein ropivacaine concentrations were within safe limits. The test dose of 3 ml of 0.75% ropivacaine was unreliable in detecting intravascular catheter placement.

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Serum concentrations of bupivacaine during prolonged continuous paravertebral infusion in young infants

S. L. W. CHEUNG, P. D. BOOKER, R. FRANKS AND M. POZZI

Summary

We have studied the efficacy of prolonged, continuous paravertebral infusion of bupivacaine for the management of post-thoracotomy pain in 22 infants with a median age of 1.5 weeks (range 1 day to 20.4 weeks). Immediately before chest closure, 0.25% bupivacaine 1.25 mg kg^{-1} was given into an extrapleural paravertebral catheter, inserted under direct vision. Subsequently, 0.125% bupivacaine with adrenaline 1:400 000 was infused at a rate of 0.2 ml kg^{-1} h^{-1} for 48 h. We confirmed that extrapleural paravertebral catheter placement under direct vision was easy in neonates and infants. The technique provided effective postoperative pain relief in 86% of patients, with three patients requiring morphine in addition. Mean serum concentration of bupivacaine after 48 h was 1.60 (0.67) μg ml^{-1}, but bupivacaine concentrations >3 μg ml^{-1} were found in three patients at 30–48 h. There were no major complications relating to the technique, and paravertebral block was an effective method of providing prolonged post-thoracotomy analgesia in these young infants. (*Br. J. Anaesth.* 1997; **79**: 9–13).

Key words

Anaesthetic techniques, regional, paravertebral. Anaesthetics local, bupivacaine. Anaesthesia, paediatric. Pain, postoperative. Surgery, thoracic. Infants.

Regional analgesia has become a routine part of the perioperative management of children undergoing thoracic surgery, with both paravertebral[1] and intrapleural[2] infusions of bupivacaine being advocated. However, we believe that paravertebral blocks are inherently safer for small infants because the local anaesthetic is applied more directly onto the appropriate nerve roots and the total drug dose required to provide effective analgesia should be lower than that using the less direct intrapleural approach. Nevertheless, in our previous study of 20 infants receiving an infusion of 0.25% bupivacaine 0.5 mg kg^{-1} h^{-1} into the paravertebral space for 24 h, we found significant cumulation of bupivacaine in some patients and maximum serum bupivacaine concentrations approached potentially toxic levels.[1]

We hypothesized that the safe duration of postoperative analgesia that could be offered using this technique may be prolonged by reducing the amount of bupivacaine being administered. Furthermore, we hoped that addition of a low concentration of adrenaline to the solution would restrict systemic absorption and thus reduce toxicity potential. The addition of adrenaline to bupivacaine, given by continuous extradural infusion to young children, has been shown to produce significant prolongation of analgesic effect.[3] Therefore, we assessed the analgesic efficacy and measured intermittently serum concentrations of bupivacaine, during infusion of bupivacaine 0.25 mg kg^{-1} h^{-1} with adrenaline 1:400 000 for 48 h, into a paravertebral catheter in infants requiring thoracotomy.

Patients and methods

The study was approved by the local Ethics Committee and written, informed parental consent was obtained. We studied 22 infants, >37 to <60 weeks gestational age (neonates included), who were >2.0 kg in weight, undergoing elective or emergency thoracotomy for various cardiac procedures.

For 14 infants no premedication was prescribed. I.v. cannulation was performed before anaesthesia which was induced with thiopentone 4 mg kg^{-1}. Atracurium 0.5 mg kg^{-1} was used to facilitate tracheal intubation. The remaining eight patients had required preoperative artificial ventilation and an i.v. infusion of morphine 10–20 μg kg^{-1} h^{-1}, the latter being stopped after induction of anaesthesia. For all patients anaesthesia was maintained subsequently with 0.5% isoflurane and 50–66% nitrous oxide in oxygen, and fentanyl 2 μg kg^{-1} i.v. was used to provide peroperative analgesia. Repeated injections of atracurium 0.25 mg kg^{-1} were given as necessary to maintain neuromuscular block. Intra-arterial and central venous cannulation were used to facilitate arterial pressure monitoring and blood sampling for bupivacaine assays. A blood sample was also obtained after induction of anaesthesia for baseline measurement of serum bupivacaine concentration (zero control).

S. L. W. CHEUNG*, FANZCA, P. D. BOOKER, FRCA, R. FRANKS, FRCS, M. POZZI, MD, Royal Liverpool Children's NHS Trust, Eaton Road, Liverpool L12 2AP. Accepted for publication: March 10, 1997.

*Present address: Department of Anaesthesia, Hospital for Sick Children, University Avenue, Toronto, Ontario, Canada.

When the surgical procedure was completed, just before chest closure, the parietal pleura was peeled medially starting at the thoracotomy space. The resulting pocket was extended from the posterior wound margin onto the vertebral bodies and for two intercostal spaces above and below using a Lahey's forceps to create a tunnel in the paravertebral space. A Tuohy needle was inserted percutaneously at a site close to the angle of the rib, near the incision, to emerge near the extrapleural pocket created earlier. The stylet was removed and a side holed (od 0.9 mm) extradural catheter (Minipack, Portex Ltd) was advanced through the needle and positioned cranially under direct vision such that approximately 3 cm of its length lay against the costo-vertebral joints within the pocket, as described previously.[1] The needle was removed and the parietal pleura was re-attached, along the posterior edge of the wound, before the thorax was closed. The catheter was aspirated and a test dose of 0.125% bupivacaine 1.0–1.5 ml with adrenaline 1:400 000 was administered through a bacterial filter. If haemodynamic variables remained stable, a loading dose of 0.25% bupivacaine 0.5 ml kg^{-1} (1.25 mg kg^{-1}) was injected into the catheter over 1 min. An infusion of 0.125% bupivacaine with adrenaline 1:400 000 at a rate of 0.2 ml kg^{-1} h^{-1} (0.25 mg kg^{-1} h^{-1}) was then started and continued for 48 h at the same rate.

All patients were nursed after operation in the ICU and the trachea was extubated when spontaneous ventilation was deemed adequate and there were no medical or surgical contraindications. Before extubation, a simplified CRIES pain score[4], excluding the crying variable, was performed by an ICU nurse as part of the routine hourly observations. When the trachea was extubated, assessments of postoperative pain were made using the full CRIES pain scale, although throughout the study the scoring for "requirement for oxygen" was modified such that the expected (baseline) oxygen saturation achieved during anaesthesia after surgery, with 30–50% oxygen, was used to assess subsequent *changes* in oxygen requirements required to achieve this baseline level. In the first 24 h after operation an i.v. infusion of morphine 10 μg kg^{-1} h^{-1} was prescribed as "rescue analgesia" but given only if a pain score >3/10 was observed and could not be reduced by a dummy or feeding. Every patient was given paracetamol 15 mg kg^{-1} via a nasogastric tube, every 6 h, from 24 to 72 h after operation.

Blood samples were obtained from a central venous or arterial cannula at 6-hourly intervals after starting the infusion, for subsequent measurement of serum concentrations of bupivacaine. An additional sample was obtained 6 h after stopping the infusion. Blood samples were centrifuged, serum separated and stored at −20 °C before assay. Serum concentrations of bupivacaine were measured by reverse phase high pressure liquid chromatography, as described previously.[1]

Results

Patient age, weight and operations are shown in table 1. Median age was 1.5 (0.1–20.4) weeks and median weight 3.2 (2.5–5.5) kg. Insertion of the extradural paravertebral catheter was not technically difficult, even in the smallest neonate. There were no major complications or adverse haemodynamic effects related to either catheter insertion or production of paravertebral block in any patient. Two patients had significant leakage of pleural fluid at the skin entry point of the paravertebral catheter, without compromise to analgesia. Another two patients had transient, accidental disconnection of the infusion. In seven babies the trachea was extubated within 1 h of surgery; in the other 15 babies the trachea remained intubated (without paralysis) for a median time of 24.0 (3–48) h after surgery.

Table 1 Individual patient data. PDA=Ligation/division of ductus arteriosus, MBTS=modified Blalock–Taussig shunt, COARC=repair of coarctation, PLIC=plication of diaphragm, PAB=pulmonary artery banding

Patient No.	Age (weeks)	Weight (kg)	Operation
1	0.9	2.8	MBTS
2	0.4	3.1	COARC
3	4.0	3.2	COARC
4	13.1	3.2	MBTS
5	0.7	3.0	PAB
6	17.0	3.8	MBTS
7	6.9	2.8	PDA
8	6.0	3.0	COARC
9	1.3	2.6	COARC
10	9.4	3.0	COARC
11	10.0	2.5	PLIC
12	1.4	3.0	COARC
13	0.3	3.7	MBTS
14	1.6	3.5	COARC
15	2.0	3.6	COARC
16	20.4	5.5	MBTS
17	0.3	3.0	MBTS
18	8.4	4.2	MBTS
19	0.1	3.1	MBTS
20	0.6	4.1	MBTS
21	1.4	3.8	COARC
22	0.1	3.2	MBTS
Median (range)	1.5 (0.1–20.4)	3.2 (2.5–5.5)	

One patient was given morphine soon after return to the ICU because extra sedation and analgesia were needed during treatment of surgical

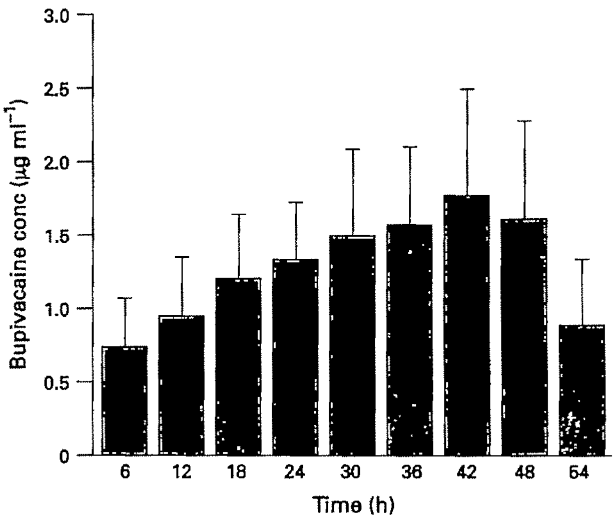

Figure 1 Mean (SD) serum bupivacaine concentrations during infusion.

Table 2 Mean (SD) serum bupivacaine concentrations during continuous infusion of 0.125% bupivacaine with adrenaline 1:400 000 at a rate of 0.25 mg kg^{-1} h^{-1}

Time (h) from starting infusion	Bupivacaine concentration (μg ml^{-1})
6	0.74 (0.33)
12	0.95 (0 40)
18	1.21 (0.44)
24	1.33 (0.40)
30	1.50 (0.59)
36	1.57 (0.53)
42	1.76 (0.72)
48	1.60 (0.67)
54	0.88 (0.44)

complications. In 18 patients the median mean hourly pain score was 0.29 (0.00–1.63); three patients had pain scores >3/10 and required morphine as rescue analgesia soon after operation. In one of these three patients a short period of accidental disconnection was associated with low bupivacaine concentrations. A second patient was subsequently diagnosed, by endoscopy, to have had severe gastritis. There was no obvious reason why the block did not work in the third patient.

Technical problems prevented sampling in one patient. There was a progressive increase in serum bupivacaine concentrations during the infusion period in most patients (fig. 1). Mean serum bupivacaine concentrations measured during the infusion period demonstrated wide variation between patients (table 2). Mean maximum serum bupivacaine concentration measured at any time after starting the infusion was 1.65 (0.47) μg ml^{-1} in 18 of 21 patients. Three patients had maximum bupivacaine concentrations of 3.29, 3.14 and 3.21 μg ml^{-1} at 30, 42 and 48 h, respectively. No patient exhibited clinical signs suggestive of bupivacaine toxicity.

Discussion

We have confirmed that direct placement of a paravertebral catheter at the time of a thoracotomy was simple, even in small neonates. Continuous infusion of bupivacaine into the catheter provided good analgesia in the great majority of patients for 48 h after operation. However, the analgesic efficacy of the technique was slightly less than that found in our previous study, where we used a higher dose of bupivacaine.[1] Four patients (18.2%) required morphine as additional analgesia during the early postoperative period, although one of these received morphine not because of block failure but because of surgical complications requiring immediate intervention.

The highest serum bupivacaine concentration reported in our previous study of similar aged infants, using an infusion of bupivacaine 0.5 mg kg^{-1} h^{-1} for 24 h, was 3.14 μg ml^{-1}, with a mean maximum concentration of 2.0 μg ml^{-1}.[1] We believe that these bupivacaine concentrations are potentially toxic[5–10] and, as we wished to provide effective analgesia for at least 48 h without undue risk, we used an infusion at half the original drug concentration, although with the same infusion rate, and with the addition of adrenaline. This new dosage regimen is similar to that suggested for caudal extradural analgesia in infants.[11] We used the same loading dose of 0.25% bupivacaine as in our previous study (1.25 mg kg^{-1}), as we know that this dose does not lead to dangerously high concentrations (mean peak 1.03 (0.56) μg ml^{-1}). Furthermore, this volume of solution (0.5 ml kg^{-1}) appears necessary to cover reliably at least five intercostal segments, which is usually required for adequate post-thoracotomy analgesia.[12] In this study the reduced bupivacaine dosage resulted in maximum serum concentrations that were well below potentially toxic concentrations in 18 infants. However, in three patients bupivacaine concentrations >3 μg ml^{-1} were measured at 30–42 h of infusion. One of the three patients with high bupivacaine concentrations required additional analgesia soon after surgery and perhaps exceptional vascularity of the paravertebral space, resulting in increased systemic absorption, may help explain these unexpected findings. It would appear, therefore, that prolonged infusion of bupivacaine for >30 h in young infants may result in high serum bupivacaine concentrations in a small, but unpredictable, proportion. However, the normal postoperative increase in plasma α_1-acid glycoprotein (AAG) concentration[13] may limit the potential toxicity of accumulating total bupivacaine by limiting the free bupivacaine concentration.[14]

However, the relationship between plasma AAG concentration, unbound bupivacaine concentration and toxicity is more complex than is immediately apparent.[14–17] Bupivacaine has a large volume of distribution (approximately 2.5 litre kg^{-1}).[18] Under conditions of near steady state, as when systemic drug absorption is gradual during bupivacaine infusion into the paravertebral space, only a small fraction of total drug dose is confined to the blood. Under these conditions, changes in AAG concentrations may have little impact on toxicity as plasma protein binding does not control access of drug to sites of toxicity.[14] Furthermore, for drugs such as bupivacaine which have a low hepatic extraction ratio, any increase in free drug concentration may be compensated by faster elimination.

Significant differences between arterial and venous local anaesthetic concentrations have been shown within the first hour of a laryngeal spray[19] or single caudal,[20] extradural[21] or intercostal injection.[21 22] This occurs because the lung *temporarily* sequestrates a large quantity of the local anaesthetic, because of a high lung–blood coefficient, before subsequent release.[16] It follows that patients with intracardiac right-to-left shunts may be at higher risk of CNS toxicity than normal patients, after accidental i.v. injection of bupivacaine. Animal experimental work has supported this premise.[23 24] However, in our study, in all patients with significant right-to-left intracardiac shunting, pulmonary blood flow was at least partially restored by the formation of a subclavian artery–pulmonary artery shunt. More importantly, however, in all of the studies mentioned above reporting simultaneous arterial and venous local anaesthetic concentrations, arterio-venous differences had become insignificant by 30–60 min after injection. In our study, we have postulated that by the time of the first sample at 6 h, near steady state conditions prevailed, and any difference between arterial and central venous bupivacaine concentrations would be insignificant.

Bupivacaine binds to erythrocytic components and also plasma proteins, and the blood–plasma bupivacaine concentration ratio (λ) varies with packed cell volume (PCV).[22] However, because of the perioperative transfusion policy, postoperative PCV of our patients did not vary widely (0.33–0.44). λ may be related to PCV by the equation $\lambda = -0.0079\ \mathrm{PCV} + 1.028$,[22] so that calculated total blood bupivacaine concentrations varied from 23 to 31% higher than our reported serum concentrations. Thus the variation in PCV in our patients resulted in a maximum inaccuracy in calculated total bupivacaine concentrations of approximately 8%. However, by using the same analytical technique as in our first study, we have been able to compare directly our present results with previous data.

We had hypothesized that the provision of adequate postoperative analgesia, without recourse to opioid medication, would enable earlier tracheal extubation than would otherwise have been the case. Eight of the patients we studied required controlled ventilation before operation and, subsequently, for 26.3 (9.4) h after operation. Retrospective data obtained from five consecutive infants having repair of coarctation who required artificial ventilation both before and after operation, but who received morphine for analgesia, showed a mean time to extubation of 46.5 (4.5) h. Although such small numbers make any definitive conclusions unwarranted, we suggest that the duration of postoperative ventilation in infants without other medical or surgical problems may be reduced by using non-opioid rather than opioid analgesia. Seven other patients in our study required postoperative intubation for 3–48 h because of surgical complications, medical problems or excessive tracheal secretions not conducive to early extubation. Despite these babies' tracheas being intubated, our nurses were able to assess facial grimacing, movement and physiological changes, such that pain scores could be assessed.

In our study we found that the technique of continuous extrapleural paravertebral infusion of bupivacaine provided effective analgesia in 86% (18 of 21) of our patients. Our "success" rate is slightly lower than that described in previous studies in infants[1] and children,[25] which used higher doses of bupivacaine. This comparison could be interpreted to indicate that, at least in some of our patients, the dose of bupivacaine administered was too low. If this had not been a research investigation, we would have tried to increase efficacy by increasing the infusion rate, but we did not attempt this strategy in our three "failure" patients, as their serum bupivacaine concentration data would not be comparable. A temporary increase in infusion rate would appear safe within the first 24 h after operation, although after 30 h such a strategy may lead to an increased risk of toxicity. The regular addition of paracetamol would also seem a sensible adjunct to this technique. Hopefully, in the near future, this useful analgesic technique may be made even safer by the use of ropivacaine rather than bupivacaine.[26]

Acknowledgements

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Gut mucosal perfusion in infants undergoing cardiopulmonary bypass: effect of preoperative captopril

P. D. BOOKER, A. J. M. DAVIS AND R. FRANKS

Summary

We have studied gut mucosal perfusion in 24 infants, aged 0.7–45 weeks, requiring cardiopulmonary bypass (CPB). Group 2 patients (n=12) had received the angiotensin converting enzyme inhibitor captopril 0.8–0.9 mg kg^{-1} orally, 45 min before induction of anaesthesia. Group 1 infants were of similar age and size and required a similar duration of CPB, but did not receive any preoperative medication. An orogastric tonometer allowed intermittent calculations of gastric intramucosal pH (pH$_i$), and rectal mucosal perfusion ("flux") was monitored using laser Doppler flowmetry. Measurements of arterial base deficit and lactate and pyruvate concentrations were made intermittently. We found no significant difference in femoral arterial pressure between the groups at any time before, during or after surgery. Similarly, we found no significant differences in our measures of regional or global tissue perfusion between the groups at any time before, during or after surgery. We conclude that preoperative administration of captopril produced no beneficial effect on gut mucosal perfusion in infants undergoing hypothermic, non-pulsatile CPB. (*Br. J. Anaesth.* 1997; **79**: 14–18).

Key words
Measurement techniques, flowmetry. Measurement techniques, tonometry. Gastrointestinal tract, mucosal perfusion. Heart, cardiopulmonary bypass. Pharmacology, captopril. Surgery, cardiovascular.

We have shown previously that infants undergoing hypothermic, non-pulsatile cardiopulmonary bypass (CPB) may demonstrate significant decreases in gut mucosal perfusion, as measured by gastric tonometry and laser Doppler flowmetry.[1] Similar significant decreases in gastric pH$_i$ have also been shown in adults during and after cardiac surgery.[2 3] Severe reductions in mucosal perfusion may be a causative factor in postoperative necrotizing enterocolitis[4] or multiple organ dysfunction.[5]

Although it is probable that multiple control mechanisms exist in the intestinal microcirculation with different mediators affecting vessels of different sizes, the renin–angiotensin system may play a pivotal role in the generation of gut hypoperfusion during CPB. Animal studies have suggested that splanchnic vessels are particularly sensitive to the vasoconstrictive effects of angiotensin II.[6 7] However, the large increase in angiotensin II concentrations induced by CPB demonstrated in adults by some workers[8] has not been a constant finding.[9 10] The reason for these different results is not known, although varying degrees of hypotension,[11] pulmonary blood flow,[12] angiotensin converting enzyme (ACE) concentrations[13] and hypothermia[9] may be relevant. No similar work has been performed in infants or children, although it has been shown that baseline renin–angiotensin activity tends to be higher in early infancy than in later childhood.[14]

Both in an animal model[15] and in healthy volunteers,[16] it has been shown that ACE inhibition causes significant splanchnic vasodilatation. ACE inhibition has been shown in an animal model to prevent splanchnic vasoconstriction and protect the gut from ischaemic injury after haemorrhage[17] and cardiogenic shock.[18] Furthermore, ACE inhibitors given in the peroperative period to adults undergoing heart surgery appear to suppress the increases in atrial natriuretic peptide, endothelin-1 and noradrenaline concentrations that would otherwise occur during and after CPB.[19]

In a prospective, controlled study, we have compared gut mucosal perfusion during CPB in infants receiving ACE inhibitors for medical reasons, with a similarly aged control group. We used a tonometric technique to assess gastric mucosal perfusion and laser Doppler flowmetry to monitor rectal mucosal perfusion.

Patients and methods

With local Ethics Committee approval and written, informed parental consent, we studied 24 infants >2.0 kg in weight, aged 0.7–45 weeks, requiring elective CPB. Twelve infants had been receiving captopril 0.8–0.9 mg kg^{-1} orally, four times a day, for at least 4 weeks before operation. Patients with coarctation and those who required vasoactive drugs other than ACE inhibitors before operation were excluded.

P. D. BOOKER, FRCA, A. J M. DAVIS, FRCA, R. FRANKS, FRCS, Royal Liverpool Children's NHS Trust, Eaton Road, Liverpool L12 2AP. Accepted for publication: March 2, 1997.

Patients in the captopril group (group 2) received their normal dose of captopril 45 min before induction of anaesthesia, on average 148 (18) min before initiation of CPB (see table 1). No premedication was given to any patient. Anaesthesia was induced with thiopentone 4 mg kg^{-1} and neuromuscular block produced with vecuronium 0.2 mg kg^{-1} h^{-1}. Anaesthesia was maintained with i.v. infusions of midazolam 240 μg kg^{-1} h^{-1} and diamorphine 24 μg kg^{-1} h^{-1}, supplemented with 0.25–0.5% isoflurane in oxygen or air, or both, before CPB. A central venous catheter was inserted and a femoral artery cannulated for monitoring systemic arterial pressure. A urinary catheter and nasopharyngeal and oesophageal temperature probes were inserted and a peripheral tissue oxygen saturation probe was taped in place.

After routine probe calibration, a laser Doppler probe (Moor Instruments Ltd) was inserted 7–8 cm into the patient's rectum, the probe's special design ensuring that its optical prism lay against the mucosa.[20] The probe was connected to a MBF3 monitor (Moor Instruments Ltd) and computer; later analysis of recordings was made using Moorsoft data interpretation software (Moor Instruments Ltd). A TRIP sigmoid tonometer (Tonometrics, Inc., MA, USA) was inserted orally into the patients stomach and connected to a Tonocap monitor (Datex UK, Ltd), which intermittently analysed $P\text{CO}_2$ in the tonometer balloon ($P\text{r}_{\text{CO}_2}$). Subsequent calculation of pH_i was made using the formula:

$$\text{pH}_\text{i}=\text{pH}+\log^{10}(P\text{a}_{\text{CO}_2}/P\text{r}_{\text{CO}_2})$$

Arterial pH and $P\text{a}_{\text{CO}_2}$ were obtained by simultaneous measurement of arterial blood-gas tensions. Correct positioning of the tonometer was aided by the sight of a small bulging of the anterior abdominal wall as it was gently advanced, later confirmed by chest x-ray taken after operation.

After sternotomy, but before manipulation of the great vessels, baseline recordings of rectal mucosal flux and femoral mean arterial pressure (MAP) were made over a 5-min period. A sample of arterial blood was obtained for measurement of pH, $P\text{a}_{\text{O}_2}$, $P\text{a}_{\text{CO}_2}$, ionic calcium (Ca^{2+}), haematocrit (PCV) and base deficit, at the same time as a gastric tonometer $P\text{r}_{\text{CO}_2}$ measurement was made. In addition, a blood sample was obtained to allow measurement of lactate and pyruvate concentrations and, subsequently, the lactate/pyruvate (L/P) ratio was calculated.

The hollow fibre D701 oxygenator (Dideco) used for CPB was primed with warmed blood and crystalloid such that blood and core temperatures 10 min after initiation of CPB were 34±0.5 °C and PCV 25±5%. When the patient had been established on non-pulsatile CPB at a flow rate of 100 ml kg^{-1} min^{-1} for 10 min and nasopharyngeal temperature remained constant to within ±0.1 °C, another arterial blood sample was obtained for measurement of PCV, base deficit, and lactate and pyruvate concentrations. MAP and rectal mucosal flux were recorded for another 5 min before the patient was cooled to 15–25 °C, depending on the anticipated duration of low flow or circulatory arrest required. The rate of cooling and rewarming was controlled to approximately 1 °C min^{-1}. Throughout CPB, PCV was maintained at 25±5% and Ca^{2+} concentration and base deficit were kept within normal limits, although no drug was given within 15 min of any observation period. Intermittent arterial blood-gas measurements were used to maintain a constant $P\text{a}_{\text{O}_2}$ (20±5 kPa) throughout CPB, aided by the use of an in-line $P\text{a}_{\text{O}_2}$ monitor (Polystan). Similarly, the Tonocap capnograph (Datex Ltd), attached to the gas outlet port of the oxygenator, helped to maintain a constant $P\text{a}_{\text{CO}_2}$ (5.3±0.5 kPa, temperature uncorrected, i.e. alpha-stat regulation). When the patient was rewarmed on CPB to 35 °C, and core temperatures remained stable to within ±0.1 °C over 5 min, another set of blood samples, flux, $P\text{r}_{\text{CO}_2}$ and haemodynamic readings were obtained.

When these rewarm readings were completed, all patients were given enoximone 1.0 mg kg^{-1} followed by infusion of 10 μg kg^{-1} min^{-1} to aid weaning from CPB. Patients undergoing an arterial switch operation also required dobutamine 10 μg kg^{-1} min^{-1} to maintain MAP >40 mm Hg after CPB. When haemodynamic variables were stable, another set of blood samples, flux, $P\text{r}_{\text{CO}_2}$ and haemodynamic readings were obtained approximately 20 and 60 min after weaning from CPB.

Before the study started we had calculated that if we studied 11 patients in each group, we should be able to detect a difference of 70 in mean flux between the groups as being significant ($P<0.05$) with a power of 90%, assuming an SD of 50. Study data have not invalidated this assumption. Comparisons between mean flux, mean pH_i, mean MAP, mean base deficit and mean L/P ratio obtained at each time (before CPB, at initial warm CPB after injection, on CPB after rewarming and after CPB) in the two groups were analysed using the Wilcoxon test and SPSS exact test. Kendall's tau-*b* rank correlation coefficient was used to assess associations between MAP, base deficit, flux, pH_i and L/P ratios at each study period.

Results

Infants in control group 1 were slightly younger and smaller than those in group 2 (tables 1, 2). Cardiopulmonary bypass (CPB) and aortic clamp times were slightly longer in group 1 than in group 2 patients, although this difference was not statistically significant. We were unable to demonstrate any significant difference between the two groups at any time, in either measure of global tissue perfusion (L/P ratio and base deficit), or regional tissue perfusion indicators (gastric pH_i and rectal mucosal flux) (tables 3–5). Similarly, there was no evidence that preoperative captopril had any effect on MAP before, during or after surgery.

There were significant correlations between arterial base deficit and pH_i at all times before and after CPB. There was also a significant correlation between our other global index of tissue hypoxia, L/P ratio, and gastric pH_i at 60 min after CPB. Anomalous correlations between L/P ratio and flux after rewarming, and between MAP and pH_i at 20

Table 1 Individual patient data. Group 1=Control, group 2=captopril given before operation. Captopril–CPB= Time from captopril administration to start of cardiopulmonary bypass (CPB). TGA=Transposition of the great arteries, VSD=ventricular septal defect, ASD=atrial septal defect, FALLOT=tetralogy of Fallot, COR TRIATR= cor triatriatum, AVSD=atrioventricular septal defect, RVOTO=right ventricular outflow obstruction, DORV,MA=double outlet right ventricle, mitral atresia, TA=tricuspid atresia

Group	Age (weeks)	Weight (kg)	Captopril–CPB (min)	Diagnosis
1	45.0	8.8	—	VSD
1	6.1	4.0	—	TGA,VSD
1	22.4	4.4	—	VSD
1	6.6	3.5	—	FALLOT
1	0.7	3.9	—	TGA
1	38.5	5.4	—	COR TRIATR
1	15.3	4.3	—	VSD
1	1.3	3.6	—	TGA
1	0.7	2.2	—	TGA
1	0.7	3.4	—	TGA
1	20.0	4.1	—	VSD
1	8.1	3.5	—	TGA
2	10.3	4.4	145	VSD
2	34.7	6.2	124	VSD
2	21.6	6.0	154	DORV,MA
2	27.6	5.8	155	VSD
2	19.6	3.9	126	VSD
2	22.0	4.6	122	AVSD
2	16.6	4.0	172	AVSD
2	15.9	2.6	141	VSD
2	21.0	4.9	155	AVSD
2	27.1	4.5	179	VSD, RVOTO
2	11.6	4.4	141	ASD,VSD
2	44.9	5.7	158	TA
Median (range)	18.1 (0.7–45.0)	4.4 (2.2–8.8)	150 (122–179)	

min after CPB, were also noted. There were no significant correlations between any of the other variables at any time.

Table 2 Age, weight, cardiopulmonary bypass (CPB) and aortic clamp (AC) times in the two groups of patients (median (range) or mean (SD))

	Group 1 (Control) (n=12)	Group 2 (Captopril) (n=12)	P
Age (weeks)	7.4 (0.7–45.0)	21.3 (10.3–44.9)	0.05
Weight (kg)	4.0 (2.2–8.8)	4.6 (2.6–6.2)	0.05
CPB time (min)	127.3 (52.1)	113.2 (23.2)	0.66
AC time (min)	64.1 (28.6)	54.6 (15.7)	0.35

Table 3 Rectal mucosal flux, gastric pH_i, mean femoral arterial pressure (MAP), base deficit and lactate/pyruvate (L/P) ratio in the two groups of patients before cardiopulmonary bypass (CPB) (mean (SD))

	Group 1 (Control) (n=12)	Group 2 (Captopril) (n=12)	P
Flux (arbitrary units)	253 (60)	247 (60)	0.92
pH_i	7.34 (0.05)	7.34 (0.10)	0.70
MAP (mm Hg)	48.5 (11.2)	44.0 (5.1)	0.43
Base deficit (mmol litre^{-1})	3.9 (2.5)	1.7 (3.2)	0.08
L/P ratio	12.1 (4.1)	12.8 (4.9)	0.93

Discussion

We were unable to demonstrate that inhibition of ACE, using captopril given before operation, increased gut mucosal perfusion in infants undergoing non-pulsatile, hypothermic CPB, compared with a matched control group. This lack of effect may have been caused by inadequate ACE inhibition, other vasoconstrictor activity may have been more influential or our methods of assessing splanchnic perfusion may have been too insensitive. However, a more likely reason for the non-significant difference between the groups may have been that gut perfusion demonstrated in the control group before, during and after CPB was normal. We have

Table 4 Mean (SD) rectal mucosal flux, gastric pH_i, mean femoral arterial pressure (MAP), arterial base deficit and lactate/pyruvate (L/P) ratio in the two groups of patients during cardiopulmonary bypass (CPB)

	At initial warm CPB period			After rewarming on CPB		
	Group 1 (Control) (n=12)	Group 2 (Captopril) (n=12)	P	Group 1 (Control) (n=12)	Group 2 (Captopril) (n=12)	P
Flux (arbitrary units)	192 (60)	177 (48)	0.73	168 (82)	131 (37)	0.47
pH_i	7.42 (0.07)	7.39 (0.08)	0.20	7.35 (0.11)	7.30 (0.11)	0.35
MAP (mm Hg)	42.3 (19.6)	37.4 (10.3)	0.70	44.1 (12.9)	48.8 (12.9)	0.35
Base deficit (mmol litre^{-1})	−0.1 (2.1)	−1.1 (2.9)	0.46	3.2 (3.2)	2.3 (4.9)	0.26
L/P ratio	19.2 (7.4)	23.8 (8.0)	0.14	30.3 (17.7)	36.0 (26.2)	0.71

Table 5 Mean (SD) rectal mucosal flux, gastric pH_i, mean femoral arterial pressure (MAP), arterial base deficit and lactate/pyruvate (L/P) ratio in the two groups of patients after cardiopulmonary bypass (CPB)

	20 min after end of CPB			60 min after end of CPB		
	Group 1 (Control) (n=12)	Group 2 (Captopril) (n=12)	P	Group 1 (Control) (n=11)	Group 2 (Captopril) (n=11)	P
Flux (arbitrary units)	168 (82)	131 (37)	0.47	256 (117)	216 (60)	0.28
pH_i	7.35 (0.11)	7.30 (0.11)	0.35	7.35 (0.09)	7.25 (0.11)	0.06
MAP (mm Hg)	44.1 (12.9)	48.8 (12.9)	0.35	50.6 (6.2)	51.4 (7.5)	0.88
Base (mmol litre^{-1})	3.2 (3.2)	2.3 (4.9)	0.26	2.5 (3.5)	4.2 (4.8)	0.40
L/P ratio	30.3 (17.7)	36.0 (26.2)	0.71	22.2 (5.8)	28.2 (8.6)	0.05

shown previously that neonates with coarctation or other aortic arch anomalies are at particular risk of gut mucosal hypoxia.[1] Although this group of patients would probably benefit most from therapy aimed at improving gut mucosal blood flow during CPB, such patients are unlikely to receive an ACE inhibitor before operation.

We made the assumption that oral administration of captopril 45 min before induction of anaesthesia would allow time for normal absorption to occur. Studies of captopril kinetics in children[21 22] suggest that the peak effect normally occurs 1.0–1.5 h after ingestion. As the duration of action of captopril is 6–10 h in children,[22] and longer in neonates, [23] it should have been exerting an inhibitory effect on angiotensin II production throughout CPB in all group 2 patients (see tables 1, 2). Nevertheless, as we did not measure angiotensin II concentrations in these patients we cannot be sure that this assumption is valid.

Arterial pressure is volume-dependent during ACE inhibition and one poorly controlled adult study suggested that after CPB vasoconstrictor requirements may be increased in patients receiving ACE inhibitors before operation.[24] However, other clinical studies in adults have been unable to demonstrate any difference between treated and untreated patients in perioperative arterial pressure or fluid requirements.[25 26] Similarly, we found no significant difference between our two groups of patients in either perioperative MAP or inotrope requirements after CPB.

Measurement of saline $P\text{CO}_2$ may be an important source of error in the assessment of gastric intramucosal pH, the error depending on the solution[27] and analyser being used.[28] Furthermore, in patients with a high tonometric $P\text{r}_{\text{CO}_2}$, saline tonometry has a tendency to underestimate the degree of tissue hypercapnia.[28 29] The Tonocap (Datex, Ltd) uses a method of measuring tissue carbon dioxide that avoids these potential inaccuracies. The Tonocap fills the TRIP (Tonometrics, Inc.) catheter balloon with air which is retained for a period of at least 15 min, to allow carbon dioxide diffusion and gas equilibration to take place. The Tonocap then withdraws a gas sample from the balloon automatically and measures $P\text{CO}_2$ using an infrared measurement technique. The Tonocap then re-injects the gas into the balloon, so that carbon dioxide depletion is reduced and faster and more complete gas equilibration is possible before the next sample is obtained. Initial studies have shown a significant correlation between results obtained using air tonometry and those obtained using conventional saline tonometry.[29 30] In accordance with the manufacturer's recommendations, we checked the accuracy of the monitor with calibration gas at least every 2 weeks or before every patient, whichever was the shorter interval. For properly calibrated monitors, the accuracy in carbon dioxide measurement, as stated by the manufacturer, is ±0.2 kPa.

To use a laser Doppler flowmetry technique to monitor mucosal blood flow it has to be assumed that a tissue measurement volume of approximately 6 mm^3 is representative of the region under examination and that there is vascular homogeneity within the tissue. Furthermore, to ensure consistency of observations from patient to patient, regular probe calibrations are necessary. We have not found that flux readings are unduly position-sensitive provided the probe is positioned such that the flux reading is the maximum that can be obtained and that a pulsatile waveform is seen. Tissue movement affects readings and this technique can only generate reproducible results in paralysed patients.

In a previous study[1] which compared infants with aortic arch obstruction with a group with normal arch anatomy, we did not find the consistent correlations between base deficit and pH_i that we found in this study. Perhaps this may be explained by the fact that patients in this study had relatively normal gut perfusion, and changes in regional perfusion reflected only changes in whole body perfusion. In our previous study, it could be assumed that the more abnormal gut perfusion seen in the study group did not reflect whole body perfusion in a consistent manner. Nevertheless, if this were the entire explanation, we should have seen similar correlations between L/P ratios and pH_i, which did not occur.

There are good reasons to suppose that gut mucosal perfusion may be enhanced after administration of captopril, as ACE inhibition not only suppresses angiotensin production but endothelin and catecholamine production are also inhibited.[19] Furthermore, ACE is identical to kininase, an enzyme that cleaves bradykinin, and increased plasma concentrations of bradykinin, a potent vasodilator, result from ACE inhibition. ACE inhibitors also increase prostaglandin E_2 synthesis,[31] decrease noradrenaline release from adrenergic nerves and adrenal medulla, and decrease vascular responsiveness to noradrenaline.[32] Nevertheless, our study has been unable to demonstrate that captopril offers any benefit, in terms of gut perfusion, to infants requiring elective CPB. However, it is possible that ACE inhibition may improve gut mucosal perfusion only in those infants who have prolonged and severe gut mucosal hypoxia, such as those with coarctation or interrupted aortic arch.

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Interactions between mivacurium and pancuronium

K. S. KIM, J. C. SHIM AND D. W. KIM

Summary

We have compared the dose–response relationships of mivacurium, pancuronium and their combination, and examined the interactions by isobolographic and fractional analyses. We studied 70 adult patients during nitrous oxide–fentanyl–propofol anaesthesia. The dose–response curves were determined by probit analysis. The ED_{95} and ED_{50} values for mivacurium were 84.2 (95% confidence interval 80.2–88.1) μg kg^{-1} and 46.2 (40.2–52.1) μg kg^{-1}, respectively. Corresponding values for pancuronium were 68.5 (63.7–73.2) μg kg^{-1} and 40.7 (35.5–45.9) μg kg^{-1}, respectively. Isobolographic and fractional analyses of the mivacurium–pancuronium combination demonstrated a synergistic interaction. An additional 30 patients were allocated randomly to receive either mivacurium 84.2 μg kg^{-1} (n=15) or pancuronium 68.5 μg kg^{-1} (n=15). When the first twitch (T1) of TOF recovered to 25%, each patient received mivacurium 46.2 μg kg^{-1}. The times after administration of mivacurium until T1 25% in the mivacurium–pancuronium group were 6.4 (3.5–9.4) min and 49.8 (44.7–54.9) min, respectively (P<0.0001). We conclude that the combination of mivacurium and pancuronium was synergistic and after pancuronium-induced neuromuscular block, mivacurium became a longer acting agent than the shorter agent. (*Br. J. Anaesth.* 1997; **79**: 19–23).

Key words
Neuromuscular block, mivacurium. Neuromuscular block, pancuronium. Neuromuscular block, measurement of response. Potency, anaesthetic, ED_{50}.

Mivacurium chloride is a short-acting, non-depolarizing neuromuscular blocking agent of the benzylisoquinoline type.[1 2] Pancuronium bromide is a long-acting, steroidal neuromuscular blocking agent and is often used when the estimated time of surgery is long.[3]

Mivacurium may be a more useful agent at the end of surgery compared with pancuronium if it retains its short-acting nature when given in combination with pancuronium. By doing this, it may be possible to maintain good clinical neuromuscular block but enable reversal in a few minutes to a safe level of recovery.

This study was undertaken to characterize the interaction of a combination of mivacurium and pancuronium in humans using the isobolographic method and to study the effects of non-depolarizing block when mivacurium was administered during recovery from pancuronium-induced neuromuscular block.

Patients and methods

After obtaining Hospital Ethics Committee approval and informed consent, we studied ASA I or II patients, aged 19–57 yr, undergoing elective surgical procedures. No patient had any disease or metabolic abnormality known to alter neuromuscular transmission, or was receiving any drug known or suspected of interfering with neuromuscular function. ECG, pulse oximetry and non-invasive arterial pressure were monitored. Palm skin temperature of the hand, where neuromuscular function was monitored, was maintained at >33 °C.

INTERACTION STUDIES

Anaesthesia was induced with fentanyl 4–5 μg kg^{-1}, propofol 2–2.5 mg kg^{-1} and 70% nitrous oxide in oxygen, and maintained with a continuous infusion of propofol 8–10 mg kg^{-1} h^{-1} and 70% nitrous oxide in oxygen supplemented with intermittent bolus doses of fentanyl 1–2 μg kg^{-1}. Ventilation was adjusted to maintain normocapnia (end-tidal carbon dioxide partial pressure 4.9–5.5 kPa).

The ulnar nerve was stimulated at the wrist with square-wave supramaximal stimuli of 0.2 ms duration, delivered in a train-of-four (TOF) sequence at 2 Hz every 10 s, using a Myotest DBS peripheral nerve stimulator (Biometer Co., Odense, Denmark). The resultant contraction of the adductor pollicis was recorded using a force displacement transducer and neuromuscular function analyser (Myograph 2000, Biometer Co., Odense, Denmark). Preload tension of the thumb was maintained at 300 g throughout the investigation. The first twitch (T1) of the TOF was considered twitch height.

After stable recording of neuromuscular transmission had been established for a minimum of 30 min, we created dose–response curves for mivacurium, pancuronium and the combination of mivacurium

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KYO SANG KIM, MD, PHD, JAE CHOL SHIM, MD, PHD, DONG WON KIM, MD, Department of Anaesthesiology, College of Medicine, Hanyang University Hospital, #17 Haengdang dong, Songdong-Ku, Seoul 133–792, Korea. Accepted for publication: March 6, 1997.

Correspondence to K. S. K.

and pancuronium. For mivacurium, we used a single-dose method because mivacurium is short-acting.[4] A subgroup of 30 patients was allocated randomly to receive mivacurium 30, 45 or 60 $\mu g\ kg^{-1}$ (10 patients for each dose). After administration of mivacurium, maximal twitch depression was assessed and anaesthesia was continued thereafter. The percentage values for twitch depression in each dose were transformed to probits and plotted against the logarithm of the dose. Subsequently, dose–response curves were obtained by least square linear regression analysis of the log-dose and probit-response values.[5]

Another subgroup of 20 patients received pancuronium in incremental doses to establish cumulative dose–response curves for pancuronium.[6] Patients received pancuronium 30 $\mu g\ kg^{-1}$ as their first dose of neuromuscular blocker. Incremental doses (15 $\mu g\ kg^{-1}$) were administered when twitch height remained constant for three consecutive twitches. After approximately 95% depression after the last incremental dose, anaesthesia was continued as required. The percentage values for twitch depression were transformed to probit means. The cumulative dose–response curve was determined by log–probit transformation of the data. From the dose–response curves of mivacurium and pancuronium administered alone, the respective ED_{95} and ED_{50} (effective dose resulting in 95% and 50% reduction in T1) values were determined.

The following predetermined doses of drugs were administered to another subgroup (20 patients): mivacurium and pancuronium, respectively, 13.9 and 12.2 $\mu g\ kg^{-1}$, 18.5 and 16.3 $\mu g\ kg^{-1}$, and 23.1 and 20.4 $\mu g\ kg^{-1}$. Studies of the single-drug groups were concluded first, so that doses of the combination could be planned. From the dose–response curves of the neuromuscular agents administered alone, we determined the respective ED_{50}. Subsequently, dose–response curves were obtained by administration of the drug combinations in a constant dose ratio based on the ED_{50} values of the single agent.

For the mivacurium–pancuronium combination, the following combinations after a pilot study were administered: 0.3 ED_{50} mivacurium +0.3 ED_{50} pancuronium; 0.4 ED_{50} mivacurium +0.4 ED_{50} pancuronium; and 0.5 ED_{50} mivacurium +0.5 ED_{50} pancuronium. Regression lines were compared using analysis of covariance.

All drugs were injected over 5 s into a rapidly flowing i.v. infusion. In the combination group, drugs were injected simultaneously into two separate i.v. cannulae inserted in one arm.

Isobolographic analysis[7 8] was used to define the type of interaction between mivacurium and pancuronium. This analysis has the advantage of being independent of the slopes of the dose–response curves, that is parallelism does not have to be established. It was used to confirm the interactions between neuromuscular blocking agents.[9–12] If the ED_{50} of a combination falls on the theoretical additive line, the effect of the drug mixture is additive. Points to the left of the theoretical additive line would be consistent with a synergistic interaction, whereas points to the right of the line would indicate an antagonistic interaction. Confidence intervals for each points were calculated from the variances of each component alone and were evaluated for statistical significance using the unpaired Student's *t* test.

Fractional analysis[13] was based on the expression of the component doses of the two agents for the combination as fractions of the doses that produce the same effect when given separately. Values near 1 indicate additive interaction, values greater than 1 imply antagonism and values less than 1 indicate synergism. This analysis was also used to confirm the interaction between neuromuscular blocking agents.[10–12]

CLINICAL STUDIES

Selection of patients, anaesthesia and preparation for the study were similar to those described in the interaction studies. After stable recording of neuromuscular transmission for a minimum of 30 min, 30 patients were allocated randomly to receive mivacurium followed by mivacurium, or pancuronium followed by mivacurium. An ED_{95} dose of mivacurium (84.2 $\mu g\ kg^{-1}$) or pancuronium (68.5 $\mu g\ kg^{-1}$) from the interaction studies was administered. If 90% neuromuscular block was not achieved, an additional dose (20 $\mu g\ kg^{-1}$) of mivacurium or pancuronium was given. Tracheal intubation was performed when neuromuscular block exceeded 95%. When the T1 response recovered to 25% after mivacurium or pancuronium, each patient received a dose of mivacurium equivalent to the ED_{50} (46.2 $\mu g\ kg^{-1}$), determined from the interaction studies. Thereafter, full spontaneous recovery of neuromuscular function was recorded in every patient. The criteria for full recovery were steady-state recovery of T1 response and a TOF ratio >0.7. Thereafter, anaesthesia was continued as indicated by individual patient care.

After mivacurium 46.2 $\mu g\ kg^{-1}$, the time from administration to maximal block was measured, and times to 1%, 25%, 75% and 95% recovery of T1 response, and the recovery index (T1 recovery from 25% to 75%) were recorded. The time from administration of mivacurium 46.2 $\mu g\ kg^{-1}$ to recovery of a TOF ratio of 0.7 was analysed.

For statistical analysis, linear regression analysis, analysis of covariance, unpaired Student's *t* test and analysis of variance were used. Unless otherwise specified, the results are expressed as mean (95% confidence intervals) and were considered significant when $P<0.05$.

Results

INTERACTION STUDIES

Patient characteristics did not differ between groups (table 1). Calculated doses for ED_{50} values for twitch depression were 46.2 (95% confidence interval 40.2–52.1) $\mu g\ kg^{-1}$ and 40.7 (35.5–45.9) $\mu g\ kg^{-1}$ for mivacurium and pancuronium, respectively. Corresponding ED_{95} values were 84.2 (80.2–88.1) $\mu g\ kg^{-1}$ and 68.5 (63.7–73.2) $\mu g\ kg^{-1}$, respectively.

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Table 1 Patient characteristics (mean (range or SD) or number). Mi=Pa=Combination of mivacurium and pancuronium; Mi-Mi=mivacurium followed by mivacurium; Pa-Mi=pancuronium followed by mivacurium

	Mivacurium	Pancuronium	Mi=Pa	Mi-Mi	Pa-Mi
Age (yr)	38.2 (21–54)	40.2 (25–55)	36.9 (20–53)	39.1 (23–57)	37.7 (19–56)
Weight (kg)	65.7 (10.8)	60.9 (9.9)	63.7 (11.2)	64.8 (10.9)	69.2 (12.1)
Height (cm)	164.8 (11.7)	162.2 (10.6)	167.2 (11.5)	165.7 (12.3)	169.4 (12.4)
Sex (M/F)	16/14	8/12	11/9	8/7	9/6

Table 2 Equipotent doses (ED_{50}) and 95% confidence intervals for mivacurium and pancuronium administered alone and in combination in a fixed-dose ratio

	Mivacurium component		Pancuronium component		
	Fraction of ED_{50}	Dose ($\mu g\ kg^{-1}$)	Fraction of ED_{50}	Dose ($\mu g\ kg^{-1}$)	Sum of fraction
Mivacurium	1	46.2 (40.2–52.1)	—	—	1
Pancuronium	—	—	1	40.7 (35.5–45.9)	1
Combination	0.19	8.8 (5.7–11.9)	0.19	7.7 (5.9–9.5)	0.38

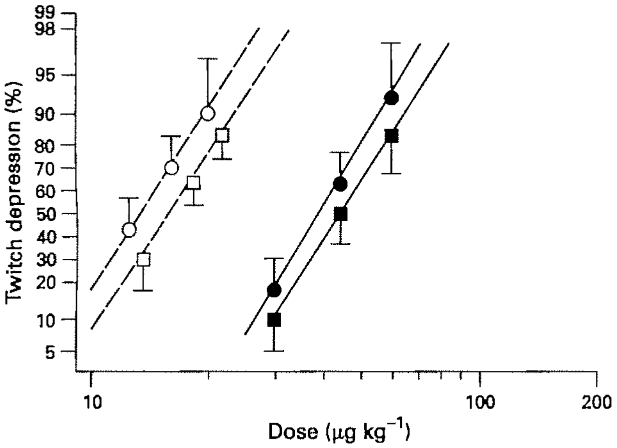

Figure 1 Log dose–probit plot for twitch depression for mivacurium with (☐) or without (■) pancuronium, and pancuronium with (○) or without (●) mivacurium. Individual points represent mean (95% confidence intervals) twitch depression (% control) with each dose.

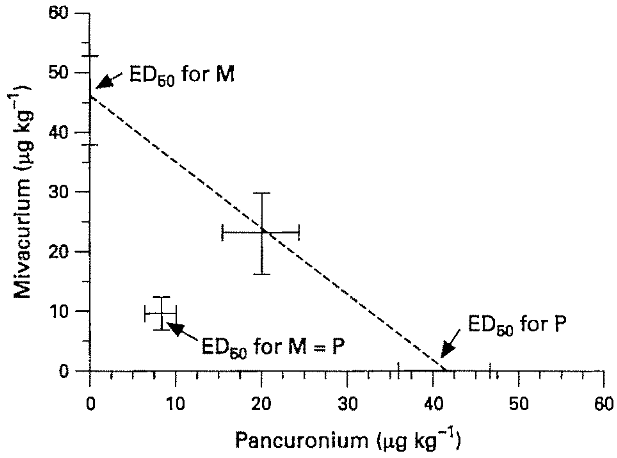

Figure 2 First twitch ED_{50} isobologram for the interaction of mivacurium (M) and pancuronium (P). The broken line connecting the single drug ED_{50} points is the theoretical additive line; the point on this line is the theoretical additive points (95% confidence intervals). The experimentally determined ED_{50} dose (95% confidence intervals) of the mivacurium–pancuronium (M=P) combination showed significantly synergistic effects ($P<0.0001$).

The dose–response curves are shown in figure 1. The slopes for mivacurium alone, pancuronium alone, mivacurium combined with pancuronium and pancuronium combined with mivacurium were, respectively, 3.1 (2.8–3.4), 3.4 (2.9–3.9), 2.8 (2.5–3.2) and 3.0 (2.6–3.4). The slopes were not significantly different. Isobolographic analysis demonstrated synergistic interactions with respect to the neuromuscular blocking activity of the mivacurium–pancuronium combination (fig. 2).

The experimentally determined ED_{50} value for the combination was 8.8 (5.7–11.9) $\mu g\ kg^{-1}$ for mivacurium and 7.7 (5.9–9.5) $\mu g\ kg^{-1}$ for pancuronium. The theoretical additive ED_{50} value was calculated as 23.1 (17.2–29.1) $\mu g\ kg^{-1}$ for mivacurium and 20.4 (16.9–23.9) $\mu g\ kg^{-1}$ for pancuronium. The confidence intervals of these points did not overlap and the result of Student's *t* test for potency ratio was significant ($P<0.0001$). Fractional analysis of this interaction also demonstrated synergism (table 2).

CLINICAL STUDIES

After mivacurium 88.1 (81.3–94.9) $\mu g\ kg^{-1}$, there was 97 (94–99) % neuromuscular block. After pancuronium 70.8 (64.5–77.1) $\mu g\ kg^{-1}$, there was 96 (93–99) % neuromuscular block. The time course of mivacurium-induced neuromuscular block in the different groups are presented in figure 3. Onset times to maximum block after mivacurium 46.2 $\mu g\ kg^{-1}$ did not differ between the mivacurium (138.2 (109.3–167.1) s) and pancuronium (101.4 (79.2–123.6) s) groups, but there was a rapid onset time in the pancuronium group. The times after mivacurium 46.2 $\mu g\ kg^{-1}$ until T1 25% recovery (clinical duration) in the mivacurium and pancuronium groups were 6.4 (3.5–9.4) min and 49.8 (44.7–54.9) min, respectively ($P<0.0001$). Corresponding times until T1 95% recovery were 12.7 (10–15.4) min and 90.2 (83.1–97.3) min, respectively ($P<0.0001$). Corresponding recovery indexes were 4.7 (3.9–5.5) min and 21.8 (18.7–24.9) min, respectively ($P<0.0001$). Corresponding times until a TOF ratio of 0.7 were 14.2 (11.1–17.3) min and 103.4 (94.3–112.5) min, respectively ($P<0.0001$).

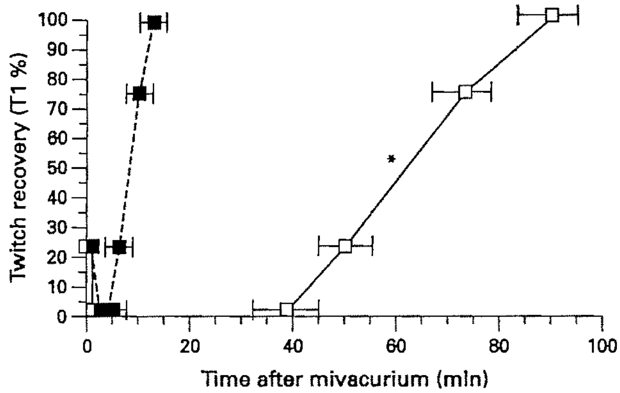

Figure 3 Spontaneous first twitch (T1) recovery of train-of-four after mivacurium 46.2 μg kg^{-1} given at T1 25% during recovery from mivacurium (■) or pancuronium (□) block. Groups differed from each other with the exception of onset time (*$P<0.0001$) Individual points represent mean (95% confidence intervals) time after mivacurium.

Discussion

Using isobolographic analysis, we have demonstrated that the combination of mivacurium and pancuronium exerted greater synergistic effect than that seen with either agent administered alone. Fractional analysis of this interaction also demonstrated a synergistic interaction, that is the effect of the combination was precisely that expected from the dose–response relationships of the individual agents. The clinical duration of action of mivacurium 46.2 μg kg^{-1} given after mivacurium was 6.4 min, while after pancuronium this mivacurium dose prolonged the clinical duration eight-fold to 49.8 min.

In this study, the calculated first twitch ED$_{50}$ and ED$_{95}$ values for mivacurium during nitrous oxide–fentanyl–propofol anaesthesia were 46.2 (40.2–52.1) μg kg^{-1} and 84.2 (80.2–88.1) μg kg^{-1}, respectively. Similar values (52 and 81 μg kg^{-1}, respectively) were reported by Savarese and colleagues[2] and by Rautoma, Erkola and Meretoja[14] (57.7 and 104.4 μg kg^{-1}, respectively) for nitrous oxide–opioid and thiopentone or propofol anaesthesia. The ED$_{50}$ and ED$_{95}$ values of 40.7 (35.5–45.9) and 68.5 (63.7–73.2) μg kg^{-1}, respectively, for pancuronium calculated in this study were in close agreement (35.7 (31.9–39.8) and 64.4 (57.5–71.8) μg kg^{-1}, respectively) with those reported by Gramstad and Lilleaasen,[15] Foldes and colleagues[16] (33 and 49 μg kg^{-1}, respectively) and Rautoma, Erkola and Meretoja[14] (37.1 and 64.8 μg kg^{-1}, respectively) during nitrous oxide–opioid and thiopentone or propofol anaesthesia. The dose–response curve for pancuronium was not significantly steeper than that for mivacurium, which is in agreement with a previous report.[14]

Synergism between mivacurium and pancuronium may exist in children[17] and adults,[14,18] but we could not find any isobolographic or fractional analyses of the mivacurium–pancuronium combination. The structural similarity or dissimilarity between the interacting neuromuscular blocking agents may have an effect.[19] Combinations of structurally similar neuromuscular blocking drugs (pipecuronium and vecuronium, rocuronium and other aminosteroids, atracurium and mivacurium) produce an additive response in isobolographic analyses.[9–11] Structurally different blockers may potentiate each other more than structurally similar blockers.[14,19,20]

Rautoma, Erkola and Meretoja[14] reported that the combined use of mivacurium and pancuronium could reduce their requirements by approximately 40%. In this study, the sum of fractions for the mivacurium–pancuronium combination was 0.38 compared with the ED$_{50}$ value of mivacurium or pancuronium (table 2). This combination could reduce requirements by 62%. The methodological difference between the study of Rautoma, Erkola and Meretoja and the present investigation is only a combination of 0.5 times the ED$_{50}$ of mivacurium and pancuronium. But we obtained the ED$_{50}$ for the combination of drugs from the dose–response curves (fig. 1) analysed by isobolographic and fractional analyses (fig. 2, table 2). In another study where atracurium and vecuronium were used together, the maximal reduction in drug consumption was approximately 30%.[21]

Synergism between mivacurium and pancuronium (which have dissimilar molecular structures) may be related to their differential actions on pre- and postsynaptic acetylcholine receptors,[19] differential sensitivity of the α-subunit acetylcholine recognition sites[22] and effects on plasma cholinesterase.[23]

In a study in which mivacurium 70 μg kg^{-1} was given at T1 25% during recovery from pancuronium block, the clinical duration was prolonged from 10 to 54 min compared with that after mivacurium block alone.[18] In this study, we also obtained similar changes in clinical duration (from 6.4 (3.5–9.4) min to 49.8 (44.7–54.9) min) for a mivacurium dose of 46.2 μg kg^{-1}. It has been suggested that the long elimination half-life of the underlying longer acting blocker prolongs the effects of the subsequent shorter acting drug.[24]

The clinical duration of action after pancuronium 80 μg kg^{-1} was 44 (SD 10) min during nitrous oxide–opioid–thiopentone anaesthesia.[25] In this study, a similar clinical duration (49.8 (44.7–54.9) min) was obtained after mivacurium in the pancuronium group. It was suggested that after pacuronium-induced neuromuscular block, mivacurium became a longer acting agent than the shorter agent, but shorter than the longer agent. Middleton and colleagues[26] suggested that the majority of receptors remain occupied by the drug administered initially; clinical duration depends more on the kinetics of the first neuromuscular blocking drug than the subsequently administered drug.

Pancuronium is known to inhibit plasma cholinesterase which degrades mivacurium.[2,23,27] Plasma cholinesterase activity has been shown to decrease by 15% or less after pancuronium 20 μg kg^{-1}.[23] On the other hand, clinically useful doses of pancuronium have been noted to inhibit plasma cholinesterase *in vitro* to a clinically insignificant amount.[28] A small dose of pancuronium might have only minimal effects on plasma cholinesterase.[14] Therefore, we did not investigate effects on plasma cholinesterase.

We conclude that the interaction of mivacurium and pancuronium was the result of synergistic actions at the neuromuscular junction, and after pancuronium-induced neuromuscular block, mivacurium became a longer acting agent than the shorter agent.

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Blood flow and mivacurium-induced neuromuscular block at the orbicularis oculi and adductor pollicis muscles

M. ABDULATIF AND M. EL-SANABARY

Summary

We have studied the pattern of blood flow and pharmacodynamic profile of mivacurium-induced block at the adductor pollicis and orbicularis oculi muscles. We studied 30 adult patients anaesthetized with fentanyl, thiopentone, nitrous oxide–isoflurane, and mivacurium 0.2 mg kg^{-1}. Neuromuscular transmission was monitored with accelerometry (TOF Guard, Biometer, Denmark). Blood flow was measured at the two muscles with the use of a laser Doppler flowmeter (Laserflo BPM^2, Vasamedics, USA). All patients developed 100% neuromuscular block at the adductor pollicis muscle. Mean maximum neuromuscular block at the orbicularis oculi was 96.4 (SD 3.5) % (ns). Onset time, time required for 25% and 75% recovery of the first twitch in the train-of-four (T1), and a train-of-four ratio (T4/T1) of 90% at the orbicularis oculi were respectively, mean 130.4 (SD 28.5) s, 9.1 (3.2) min, 16.2 (3.9) min and 20.2 (4.3) min and were significantly shorter than the corresponding values at the adductor pollicis: 202.7 (37.2) s, 12.9 (3.9) min, 21.1 (5.1) min and 30.8 (7.4) min. For a given T1, there was significantly less train-of-four fade (T4/T1) at the orbicularis oculi than at the adductor pollicis muscle during recovery. Blood flow was comparable at the two muscles before induction of anaesthesia. Thiopentone significantly increased thenar muscle blood flow from 2.9 (1.5) to 12.3 (6.8) ml 100 g^{-1} min^{-1}, with a further increase to 22.7 (8.0) ml 100 g^{-1} min^{-1} after isoflurane ($P<0.001$). Blood flow at the orbicularis oculi was not altered by thiopentone or isoflurane and was consistently lower than that at the adductor pollicis muscle. We conclude that the different pharmacodynamic profiles of mivacurium-induced block at the orbicularis oculi and adductor pollicis muscles were not related primarily to a difference in blood flows. (*Br. J. Anaesth.* 1997; **79**: 24–28).

Key words
Neuromuscular block, mivacurium. Neuromuscular block, measurement of response. Blood, flow. Muscle skeletal. Muscle skeletal, blood flow. Measurement techniques, flowmetry.

The response to a bolus dose of a neuromuscular blocking drug depends on which muscle is examined.[1] There can be differences in both onset time and sensitivity between various muscles. For example, the orbicularis oculi tends to require a larger dose for the same degree of paralysis compared with the adductor pollicis muscle. However, onset of paralysis is faster at the former.[2–4] These two apparently contradictory effects depend on different factors. The dose required for a given effect in a specific muscle depends largely on the concentration required to block the receptors.[1] On the other hand, onset time is determined to a great extent on the rate at which the drug gains access to the receptors.[1] In dogs, the onset time of gallamine-induced neuromuscular block in the tibialis anterior muscle was found to be shortened by increasing blood flow to the muscle.[5]

Human studies correlating neuromuscular response at different muscles with blood flow are lacking. With the recent availability of laser Doppler flowmeters, continuous monitoring of microcirculatory blood flow has become possible.[6 7] Using this technique we have compared blood flow at the orbicularis oculi and adductor pollicis muscles in patients during fentanyl, thiopentone, nitrous oxide–isoflurane anaesthesia. The pharmacodynamic profile of mivacurium-induced neuromuscular block was also evaluated at the two muscles using accelerometry.

Patients and methods

We studied 30 adult male patients, ASA I or II, aged 20–50 yr (mean 36.7 yr), weighing 61–82 kg (mean 68 (SD 9.4 kg), undergoing diagnostic endoscopic surgery, for example knee arthroscopy. This study was approved by the Hospital Ethics Committee and all patients gave written informed consent. We excluded any patient suffering from cardiac, vascular, respiratory, hepatic, renal or neuromuscular disorders. Chronic smokers, patients with previous head and neck surgery, history of small joint arthritis or those receiving medications known to affect normal neuromuscular transmission were also excluded.

MOHAMED ABDULATIF*, MB, BCH, MSC, MD, MOHGA EL-SANABARY, MB, BCH, MSC, MD, Department of Anaesthesia, Faculty of Medicine, Cairo University, Egypt. Accepted for publication: March 22, 1997.

*Address for correspondence: PO Box 147, Panorama October 11811, Nasr City, Cairo, Egypt.

All patient were premedicated with oral diazepam 10–15 mg, approximately 90 min before surgery. In the operating room, lactated Ringer's solution with 5% glucose was administered at a rate of 4–6 ml kg^{-1} h^{-1} via a peripheral arm vein. The ECG was monitored continuously and arterial pressure was measured using an electronic oscillotonometer. Anaesthesia was induced in all patients with midazolam 2–3 mg, fentanyl 2 μg kg^{-1} and thiopentone 4–5 mg kg^{-1}. The airway was maintained with an appropriately sized laryngeal mask. For the first 5 min after induction, anaesthesia was maintained with 70% nitrous oxide in oxygen. This was followed by addition of 0.5–1% isoflurane end-tidal concentration to the anaesthetic mixture. Ventilation was controlled to maintain normocapnia (end-tidal carbon dioxide partial pressure 4.6–5.3 kPa). Nasopharyngeal temperature was monitored and maintained at 36–37 °C using warm blankets and heated i.v. fluids. Skin temperature over the thenar eminence and the forehead was monitored also and maintained at 32–33 °C. Concentrations of isoflurane, nitrous oxide, carbon dioxide and oxygen saturation were measured continuously by a multiple-gas analyser (Capnomac Ultima-SVI, Datex Instrumentarium Corporation, Helsinki, Finland).

The ulnar and temporal branches of the facial nerves were stimulated supramaximally with single twitch square pulses of 0.2 ms duration, repeated every 10 s. An acceleration piezoelectric transducer (Biometer International, Odense, Denmark) was fastened to the volar surface of the distal phalanx of the thumb using adhesive tape or to the upper eyelid by means of double-sided adhesive tape. At the eyelid, the piezoelectric transducer was fixed such that it measured the acceleration generated by circumferential contraction of the orbicularis oculi muscle.[4]

After at least 20 min of stable anaesthetic conditions and stabilization of the twitch height recordings, each patient received an i.v. bolus of mivacurium 0.2 mg kg^{-1}. At maximum block, the pattern of nerve stimulation was changed to a train-of-four (TOF) sequence at 2 Hz repeated every 15 s. Recording of the evoked adductor pollicis or orbicularis oculi response was carried out using a TOF Guard neuromuscular monitor (Biometer International, Odense, Denmark). All graphical and numerical neuromuscular data were recorded on a memory card and subsequently a computer printout was obtained using TOF Guard Reader software (Biometer International, Odense, Denmark). The following variables were determined for each muscle: (1) maximum twitch depression after mivacurium; (2) onset of block: time interval between the end of injection of mivacurium and development of maximum block; (3) time interval between development of maximum block and recovery of T1 to a value of 25% and 75% of its control, and recovery of train-of-four ratio (T4/T1) to a value of 90%; (4) recovery index (RI): time required for recovery of T1 from 25 to 75% of its control; (5) T1 and train-of-four ratio every 1 min for at least 30 min after development of maximum block; (6) T4/T1 ratio at 10% incremental recovery of T1.

A laser Doppler flowmeter (Laserflo BPM², Vasamedics Inc, Minnesota, USA) was used to measure blood flow at either the adductor pollicis (n=15) or the orbicularis oculi muscle (n=15). A sterile 19-gauge needle type laser flowmeter probe (Laserflo BPM², Vasamedics Inc, Minnesota, USA) was inserted percutaneously in the thenar eminence or the orbital part of the orbicularis oculi muscle. The hand and eye contralateral to the site of neuromuscular monitoring were used for blood flow measurements. Blood flow monitoring started in all patients before induction of anaesthesia and 15 min were allowed for stabilization of the flow signal. The baseline awake blood flow value was obtained as the mean of three successive readings recorded at 2-min intervals. During the course of anaesthesia, muscle blood flow was monitored continuously and recorded every 1 min for the first 10 min during induction and every 5 min during maintenance of anaesthesia.

Statistical analyses were performed by analysis of variance (for repeated measures) to compare blood flow changes within each muscle, and paired Student's t test to compare the two muscles with respect to blood flow and neuromuscular data. Differences were considered significant when $P<0.05$.

Table 1 Neuromuscular data (mean (SD))

	Orbicularis oculi	Adductor pollicis	P
Maximum twitch depression (%)	96.4 (3.5)	100	ns
Onset (s)	130.4 (28.5)	202.7 (37.2)	<0.001
T1 25% (min)	9.1 (3.2)	12.9 (3.9)	<0.01
T1 75% (min)	16.2 (3.9)	21.1 (5.1)	<0.05
Recovery index (min)	7.1 (2.2)	8.2 (1.8)	ns
T4/T1 (90%) (min)	20.2 (4.3)	30.8 (7.4)	<0.001

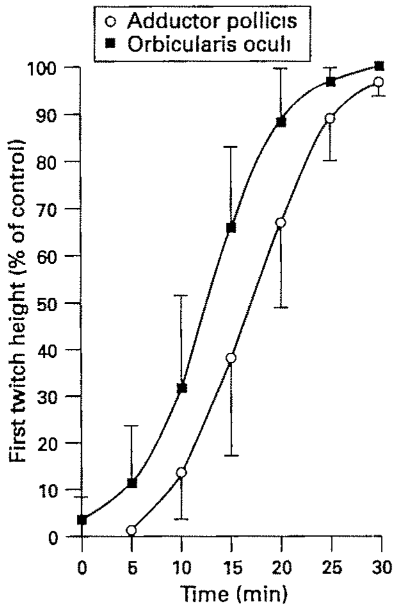

Figure 1 Time course of first twitch recovery at the orbicularis oculi and adductor pollicis muscles after mivacurium 0.2 mg kg^{-1} (mean, SD).

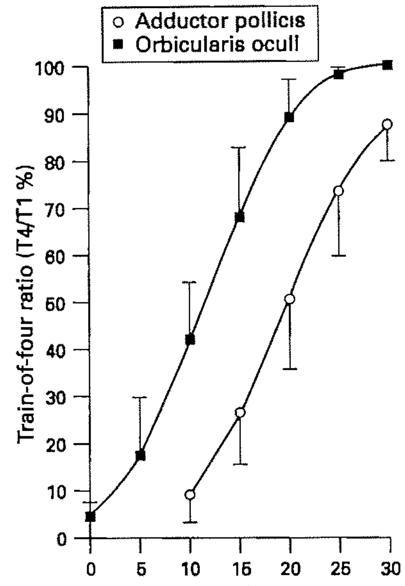

Figure 2 Time course of train-of-four ratio (T4/T1 %) recovery at the orbicularis oculi and adductor pollicis muscles after mivacurium 0.2 mg kg^{-1} (mean, SD).

Results

All patients developed 100% neuromuscular block at the adductor pollicis muscle. In contrast, neuromuscular block at the orbicularis oculi was 85–94% in seven patients. However, overall mean maximum neuromuscular block at the orbicularis oculi was 96.4 (SD 3.5) % and was not statistically different from the adductor pollicis muscle.

Onset time, time required for 25% and 75% recovery of T1, and T4/T1 ratio of 90% were all shorter for the orbicularis oculi than the adductor pollicis muscle. Recovery indices were comparable at the two muscles (table 1, figs 1, 2).

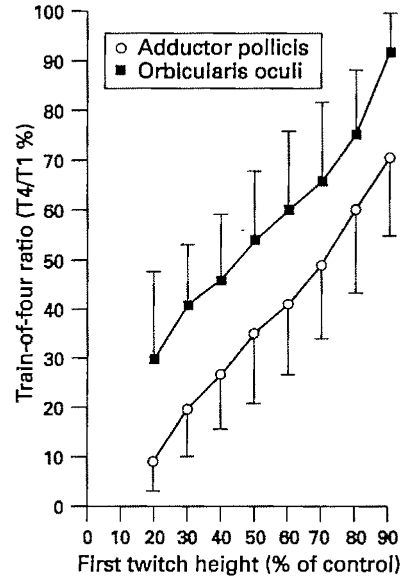

Figure 3 Relationship between first twitch recovery (% of control) and train-of-four fade (T4/T1) during recovery from mivacurium-induced neuromuscular block at the orbicularis oculi and adductor pollicis muscles (mean, SD). There was significantly less T4/T1 fade at the orbicularis oculi than at the adductor pollicis muscle throughout the course of first twitch (T1) recovery.

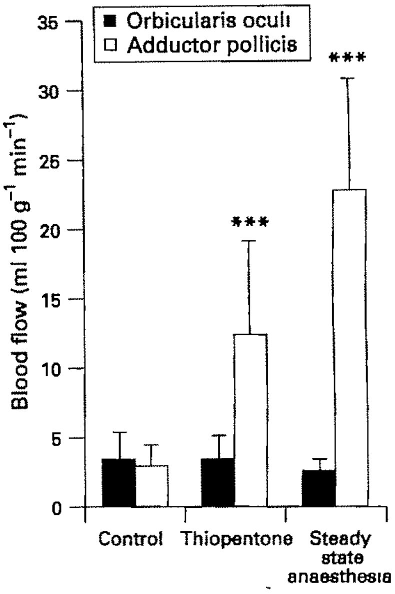

Figure 4 Blood flow pattern at the orbicularis oculi and adductor pollicis muscles before anaesthesia (control), after thiopentone, and during steady state isoflurane anaesthesia (mean, SD). ***$P<0.001$ compared with control values.

For a given T1, there was significantly less train-of-four fade (T4/T1) at the orbicularis oculi than at the adductor pollicis muscle throughout the course of neuromuscular recovery (fig. 3).

Blood flow was comparable at the two muscles before induction of anaesthesia. Thiopentone significantly increased thenar muscle blood flow from 2.9 (1.5) to 12.3 (6.8) ml 100 g^{-1} min^{-1}, with a further increase to 22.7 (8.0) ml 100 g^{-1} min^{-1} with addition of isoflurane ($P<0.001$). Blood flow at the orbicularis oculi was not altered by thiopentone or isoflurane and was consistently lower than that at the adductor pollicis muscle despite comparable haemodynamics in the two groups (fig. 4).

Temperature of the skin overlying the two muscles was comparable.

Discussion

We have confirmed the current view that the onset of non-depolarizing neuromuscular block is more rapid and its duration is shorter at the orbicularis oculi compared with the adductor pollicis muscle. The difference in onset time of mivacurium-induced block between the two muscles was, on average, 1.2 min. This is consistent with the recent findings of Rimaniol and collaegues[4] and Debaene and co-workers.[8] Onset times of neuromuscular block at the orbicularis oculi muscle reported by Rimaniol and co-workers[4], using accelerometry, were 235 and 90 s after mivacurium 0.15 mg kg^{-1} and 0.25 mg kg^{-1}, respectively. In our study, onset time of an intermediate dose of mivacurium 0.2 mg kg^{-1} at the orbicularis oculi was 130.4 s and was in general agreement with the trends in onset time reported by Rimaniol and colleagues.[4]

Neuromuscular blocking agents can only produce neuromuscular block when they bind with acetylcholine receptors at the neuromuscular junction. Therefore, onset time after injection of neuromuscular blocking drugs into a peripheral vein depends on circulatory factors, notably cardiac output, circulation time to the muscle, muscle blood flow and proximity of the target muscle to the central arterial circulation.[9,10] In this study the response of the orbicularis oculi and adductor pollicis muscles were determined simultaneously in the same group of patients. This clearly obviates the possible effect of cardiac output on the onset of block. A surprising finding in this study was that blood flow in the orbicularis oculi muscle was significantly lower than that in the adductor pollicis muscle during thiopentone–nitrous oxide–isoflurane anaesthesia. The underlying reasons for the differences in blood flow between the two muscles are unclear at this stage. However, Vollmar and Habazettl,[11] noted that the nature and magnitude of the vascular effects of anaesthetics vary depending on the vascular bed and type of vessels studied. Our blood flow results suggest that, at least for the orbicularis oculi muscle, blood flow was not the main mechanism of rapid onset of action of mivacurium-induced block. It is possible however that the proximity of the orbicularis oculi to the central circulation compared with the adductor pollicis may compensate for the difference in blood flow and may have a role in accelerating the onset of neuromuscular block at the former. The onset of vecuronium-induced neuromuscular block in the adductor pollicis muscle was more rapid when the drug was injected into the central circulation, via a pulmonary artery catheter, than when the drug was given into a peripheral vein on the hand [12].

In our study, all patients developed 100% neuromuscular block at the adductor pollicis muscle, but neuromuscular block at the orbicularis oculi was 85–94% in seven patients. These findings, coupled with a shorter duration of mivacurium-induced block at the orbicularis oculi, reflect the relative resistance of this muscle to mivacurium-induced block. Several mechanisms have been proposed to explain the unequal sensitivities of different muscles to neuromuscular blocking agents. Recent studies, however, proved that this is related mainly to mean muscle fibre diameter and the fraction of fibre circumference occupied by the motor endplate.[13] However, the association between duration of neuromuscular block and fibre size or endplate to fibre size ratio was relatively weak suggesting that other factors may contribute to muscle response to neuromuscular blockers.

Bowman[14] suggested that single twitch depression, and tetanic or train-of-four fade, are the result of interaction of acetylcholine antagonists with different binding sites within the neuromuscular junction. Neuromuscular blockers act at presynaptic nicotinic receptors in such a way that mobilization of acetylcholine is impaired. Thus during high frequency stimulation, transmitter output becomes exhausted so that fade occurs. In this study, there was significantly less train-of-four fade (T4/T1) at the orbicularis oculi than the adductor pollicis muscle throughout the course of neuromuscular recovery. It is therefore possible that resistance of the orbicularis oculi may reflect less prejunctional effects of mivacurium at this muscle than the adductor pollicis.

Current evidence suggests that interest is increasing in monitoring the response of orbicularis oculi muscle in clinical practice. This is mainly because of the comparable neuromuscular course at this muscle, the diaphragm and laryngeal muscles.[2] Force displacement transducers[15], electromyography[2] and visual assessment[8] have been used previously to monitor the orbicularis oculi response. Mechanomyography and electromyography are used mainly for research purposes. Visual assessment is simple but lacks reliability. The recent study by Rimaniol and colleagues[4] and our study have demonstrated that piezoelectric acceleration transducers could be used to monitor the mechanical response of the orbicularis oculi muscle. The new generations of acceleration monitors, for example TOF Guard, are as reliable as mechanomyography and electromyography[16,17] and their simplicity of operation may increase interest in routine neuromuscular transmission monitoring at different sites, including the orbicularis oculi muscle.

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Comparison of extradural and general anaesthesia on the fibrinolytic response to total knee arthroplasty

N. E. SHARROCK, G. GO, P. WILLIAMS-RUSSO, S. B. HAAS AND P. C. HARPEL

Summary

Extradural anaesthesia is associated with lower incidences of deep vein thrombosis after total knee arthroplasty. It is not known if the type of anaesthesia influences thrombogenesis or fibrinolysis during knee surgery performed under tourniquet. We studied 31 patients allocated randomly to receive either extradural or general anaesthesia for primary unilateral total knee arthroplasty performed under tourniquet. Radial artery blood samples were obtained before surgery, during surgery with the tourniquet inflated and on deflation of the tourniquet. Plasma samples were assayed for markers of thrombin generation and fibrinolysis. Two of the circulating indices of thrombin generation, fibrinopeptide A and thrombin–antithrombin complexes, increased to a similar degree in the perioperative period in both groups. Fibrinolytic activity was similar in both groups, as measured by tissue plasminogen activator (t-PA) antigen, t-PA activity, t-PA–plasminogen activator inhibitor complexes, α_2-plasmin inhibitor–plasmin complexes and D-dimer. Extradural and general anaesthesia did not result in significant differences in either thrombin generation or fibrinolytic activity during total knee arthroplasty performed under tourniquet. (*Br. J. Anaesth.* 1997; **79**: 29–34).

Key words
Anaesthetic techniques, extradural. Anaesthesia, general. Complications, thrombosis. Blood, coagulation. Surgery, orthopaedic.

The incidence of deep vein thrombosis (DVT) after total knee arthroplasty is reported to be lower with extradural than general anaesthesia.[1–4] The mechanism for this reduction is not known but it has been proposed that extradural anaesthesia may be associated with enhanced fibrinolysis.[1 3 5] Increased fibrinolytic activity was demonstrated in patients receiving extradural anaesthesia for total hip arthroplasty[5] and peripheral vascular surgery[6] but other studies have failed to confirm this finding.[7 8]

We examined if fibrinolysis is enhanced in the immediate perioperative period as the majority of thrombi which develop after total knee arthroplasty are evident venographically immediately after surgery.[9] Contrary to our expectation, there were no differences in either indices of thrombin generation or fibrinolysis between extradural and general anaesthesia. These data suggest that the salutary effect of extradural anaesthesia on DVT after total knee arthroplasty may be caused by other factor(s) in this early postoperative period.

Patients and methods

After obtaining Institutional Review Board approval, 31 patients diagnosed with osteoarthritis undergoing unilateral primary bicondylar cemented total knee arthroplasty consented to be allocated randomly to receive either extradural or general anaesthesia. These were a subpopulation of patients enrolled in a larger study[4] designed to compare the effects of general with extradural anaesthesia on cognitive function, adverse cardiac events and DVT after total knee arthroplasty. Patients were excluded if they had any contraindication to either extradural or general anaesthesia. Contraindications to extradural anaesthesia included ankylosing spondylitis, history of extensive Harrington rod spinal fusion to the sacrum, cancer metastases to lumbar or thoracic vertebrae, history of bleeding diathesis and local infection at the site of extradural anaesthesia. Contraindications to general anaesthesia included a history of malignant hyperthermia and unstable cervical spine. Patients were also excluded if they had been receiving anticoagulants within 1 month of surgery.

All patients discontinued aspirin 1 week before surgery and other non-steroidal anti-inflammatory medication at least 48 h before operation. Perioperative heparin was not administered and pneumatic compression boots were not used. After operation, all patient received aspirin 325 mg twice daily as the only form of thromboprophylaxis. The first dose was administered at least 4 h after surgery after all blood samples had been obtained.

NIGEL E. SHARROCK*, MB, CHB, GEORGE GO, BS (Department of Anaesthesiology); PAMELA WILLIAMS-RUSSO, MD (Department of Internal Medicine); STEVEN B. HAAS, MD (Department of Orthopaedic Surgery); Hospital for Special Surgery, Cornell University Medical College, New York, USA. PETER C. HARPEL, MD, Division of Hematology, Mount Sinai School of Medicine, New York, USA. Accepted for publication: March 10, 1997.

*Address for correspondence: Department of Anaesthesiology, The Hospital for Special Surgery, 535 East 70th Street, New York, NY 10021, USA.

ANAESTHESIA

Patients received no premedication. I.v. cannulae were inserted the evening before surgery and crystalloid infused at 50–70 ml h^{-1} before operation; 20-gauge radial artery cannulae were inserted percutaneously under local anaesthesia and patients were monitored with ECG and pulse oximetry. Patients receiving general anaesthesia also had end-tidal carbon dioxide and oesophageal temperature monitoring.

At the discretion of the anaesthetist, extradural anaesthesia was performed by injection of 15–20 ml of either 0.75% bupivacaine ($n=12$) or 2% lignocaine with adrenaline 1:300 000 ($n=3$) via a 17-gauge Tuohy needle at the L3–4 or L2–3 interspace and an extradural catheter inserted. Intraoperative haemodynamic stability was maintained with i.v. fluid and, if necessary, intermittent injections of ephedrine 3–5 mg to maintain systolic arterial pressure in the range 110–120 mm Hg. All patients received nasal oxygen 2–5 litre min^{-1} throughout surgery.

General anaesthesia was induced using fentanyl 1–3 $\mu g\ kg^{-1}$, thiopentone 2–3 mg kg^{-1}, and vecuronium 8–10 mg to facilitate tracheal intubation. Anaesthesia was maintained using isoflurane and 70% nitrous oxide in oxygen, and fentanyl up to 1 $\mu g\ kg^{-1}\ h^{-1}$. Antagonism of neuromuscular block was performed in all patients at the end of surgery and the trachea of all patients was extubated before transfer to the post-anaesthesia care unit (PACU).

SURGERY

Each procedure was performed under tourniquet; the tourniquet was inflated after exsanguination of the limb with an Esmarch bandage. After fixation of components with methylmethacrylate, the tourniquet was deflated for several minutes to achieve haemostasis; the Esmarch bandage was reapplied and the tourniquet re-inflated. At the end of surgery, the tourniquet was again deflated after the dressings were applied. All patients underwent primary total knee arthroplasty using cemented bicondylar components.

MEASUREMENTS

Blood samples were obtained from the radial artery cannula via a three-way stopcock at the following times: before induction of anaesthesia (sample 1), 20 min after the start of the surgical procedure (sample 2), 45 s after deflation of the tourniquet at the end of surgery (sample 3) and 1 h after operation in the PACU (sample 4). Continuous infusion of 3 ml h^{-1} of a solution containing unfractionated heparin 4 u. ml^{-1} in normal saline was maintained throughout surgery. Samples were obtained after 4 ml were discarded to clear the arterial cannula and prevent haemodilution. No patient received any blood products during the study period.

ASSAYS

Samples were placed in citrated tubes (sodium citrate 0.13 mol $litre^{-1}$, 9:1 volume to volume) and centrifuged at 2000 *g* for 10 min at 4 °C. Plasma samples were stored immediately at −70 °C until ready for assay. Blood for fibrinopeptide A measurement was collected in tubes containing an anticoagulant solution, provided with the Asserachrom (Diagnostica Stago, Franconville, France) fibrinopeptide A kit and treated with bentonite twice before storing at −70 °C. Measurement of fibrinopeptide A (FPA), D-dimer, thrombin–antithrombin (TAT) complex, tissue plasminogen activator (t-PA) antigen and t-PA–plasminogen activator inhibitor-1 (t-PA–PAI-1) were measured by enzyme-linked immunosorbent assay using the respective Asserachrom kits (Diagnostica Stago, Franconville, France). t-PA activity was measured using a whole plasma assay specific for t-PA as described previously.[10 11] α_2-Plasmin inhibitor–plasmin complexes (PIP) were assayed by a method described previously.[11]

DATA ANALYSIS

Differences between groups were compared using *t* tests for continuous variables, chi-square for dichotomous variables or the Mann–Whitney test for ordinal data. Differences in circulating haematological variables between groups were assessed using ANOVA, whereas paired *t* tests were used for within-group analysis. Alpha was set at 0.05.

Results

Preoperative characteristics and operative factors for patients receiving extradural anaesthesia ($n=15$) or general anaesthesia ($n=16$) were similar (table 1).

Fibrinopeptide A (FPA) (fig. 1) increased during surgery (samples 1–2) ($P=0.02$ and $P=0.07$) and

Table 1 Patient characteristics, surgery start time, duration of surgery and intraoperative i.v. fluids administered (mean (SD) or range) or number). No significant differences between groups

	General anaesthesia ($n=16$)	Extradural anaesthesia ($n=15$)
Sex (M/F)	2/14	4/11
Age (yr)	68.6 (52–82)	67.0 (55–86)
Height (cm)	166.1 (8.5)	165.8 (13.0)
Weight (kg)	86.9 (19.0)	80.2 (15.0)
ASA I/II/III	1/12/3	0/15/0
Surgery start time	12:44 (09:03–16:03)	11:40 (08:56–16:04)
Duration of surgery (min)	104.7 (43.4)	100.9 (32.0)
Intraoperative i.v. fluids (ml)	1140.6 (485.2)	1133.3 (415.2)

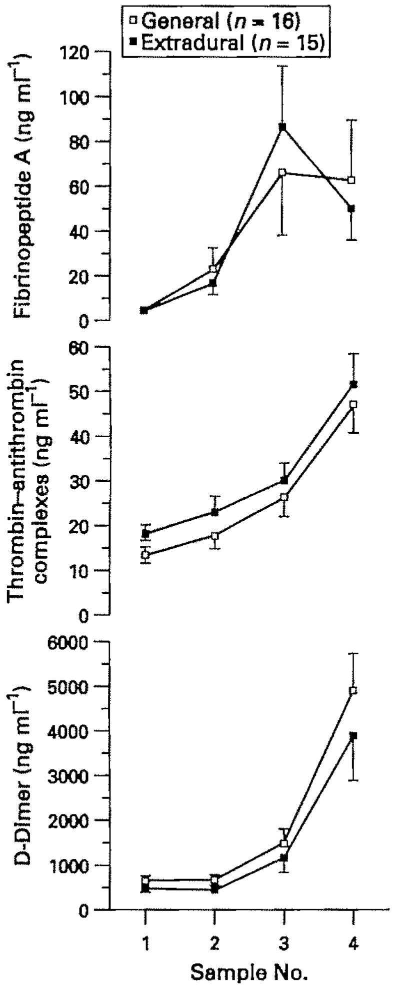

Figure 1 Fibrinopeptide A, thrombin–antithrombin complexes and D-dimer concentrations in patients receiving general or extradural anaesthesia. Measurements were made before induction of anaesthesia (sample 1), 20 min after the start of surgery (sample 2), 45 s after deflation of the tourniquet at the end of surgery (sample 3) and 1 h after operation in the PACU (sample 4). Values are mean (SEM).

also after deflation of the tourniquet at the end of surgery (samples 1–3) (P=0.01 and P=0.04) in the extradural and general anaesthesia groups, respectively. There were no significant differences between groups.

Thrombin–antithrombin complexes (TAT) (fig. 1) increased slightly during surgery with the tourniquet inflated (samples 1–2) (P=0.15 and P=0.05), but increased significantly after tourniquet deflation (samples 1–3) (P=0.002 and P=0.004) and remained increased at 1 h after surgery (samples 1–4) (P=0.0001 and P=0.0001) in the extradural and general anaesthesia groups, respectively. There were no significant differences between groups.

D-dimer (fig. 1) did not change significantly during surgery with the tourniquet inflated, but did increase significantly after deflation of the tourniquet (samples 1–3) (P=0.05 and P=0.01) and remained increased at 1 h after surgery (samples 1–4) (P=0.006 and P=0.0001) in the extradural and general anaesthesia groups, respectively. There were no significant differences between groups.

Tissue plasminogen activator (t-PA) activity (fig. 2) increased significantly with the tourniquet inflated (samples 1–2) (P=0.01 and P=0.01) and remained increased after tourniquet deflation (samples 1–3)

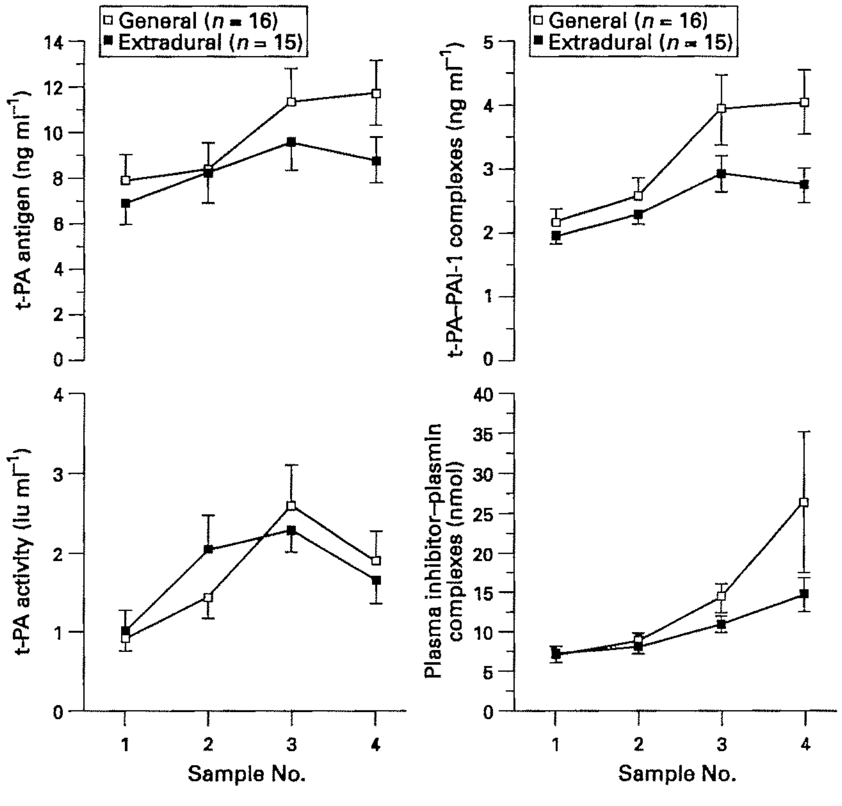

Figure 2 Tissue plasminogen activator (t-PA) antigen, t-PA activity, t-PA–plasminogen activator inhibitor-1 (t-PA–PAI-1) and α_2-plasmin inhibitor–plasmin complexes in patients receiving general or extradural anaesthesia Measurements were made before induction of anaesthesia (sample 1), 20 min after the start of surgery (sample 2), 45 s after deflation of the tourniquet at the end of surgery (sample 3) and 1 h after operation in the PACU (sample 4). Values are mean (SEM).

(P=0.0001 and P=0.001) in the extradural and general anaesthesia groups, respectively. t-PA activity declined after operation (samples 3–4) (P=0.03 and P=0.19) in the extradural and general anaesthesia groups, respectively. There were no differences between the extradural and general anaesthesia groups at any times.

Tissue plasminogen activator (t-PA) antigen, t-PA–plasminogen activator inhibitor (t-PA-PAI-1) complexes and α_2-plasmin inhibitor–plasmin (PIP) complexes (fig. 2) increased minimally with the tourniquet inflated (samples 1–2) but increased significantly after deflation of the tourniquet at the end of surgery (samples 1–3) (P<0.05). There were no significant differences between the extradural and general anaesthesia groups at any times.

The sample size of this study was sufficient to detect a significant difference in both FPA and t-PA activity equal to or greater than the SD of each measurement with a power of 0.8.

Discussion

All previous studies have shown a tendency for lower incidences of DVT in patients receiving extradural rather than general anaesthesia after total knee arthroplasty. In a small study from Sweden, incidences were 59% with general anaesthesia and 18% with extradural anaesthesia.[1] In a large retrospective study, incidences were 56% with general anaesthesia and 42% with extradural anaesthesia.[3] In a randomized, prospective study of extradural compared with general anaesthesia from which these patients were a subset, there was also a tendency towards a lower incidence of DVT with extradural anaesthesia (40% *vs* 48% for general anaesthesia).[4]

This study was designed to determine if differences in anaesthetic technique influenced the genesis of thrombosis during surgery itself. When thrombin, a serine protease, acts on fibrinogen to form fibrin, a cleavage product, fibrinopeptide A (FPA) is formed. When formed, circulating thrombin is subsequently bound to antithrombin III to form the inactive thrombin–antithrombin complexes (TAT). Concentrations of TAT and FPA are thus circulating indices of thrombin generation.[12 13] We reasoned that if more incidences of venous thrombosis were occurring during operation in patients receiving general anaesthesia, increased concentrations of FPA or TAT, or both, would be detectable in blood immediately after deflation of the tourniquet. Enhanced thrombogenesis was not observed in patients receiving general anaesthesia under tourniquet during surgery, as FPA and TAT concentrations were similar to those patients receiving extradural anaesthesia.

Immediately after the tourniquet was deflated (sample 3), significant increases in FPA and TAT were noted in both groups. These increases in TAT and FPA indicate that activation of the coagulation cascade was occurring during surgery with the tourniquet inflated and is confirmatory evidence that thrombi develop during total knee arthroplasty with the tourniquet inflated.[9 14]

Other studies have confirmed that thrombi develop in the intraoperative period during total knee arthroplasty with the tourniquet inflated. Parmet and colleagues observed showers of small emboli in the right atrium after tourniquet deflation using transoesophageal echocardiography.[14 15] Concurrently, they aspirated fresh thrombi from the femoral vein of the operated limb and from central venous catheters. Maynard, Sculco and Ghelman demonstrated that 86% of patients who went on to develop DVT after total knee arthroplasty had venographically evident thrombi in the immediate postoperative period.[9] Venous stasis,[16] hypoxia[17 18] and hypothermia led to endothelial injury in the ischaemic limb with the tourniquet inflated[19] providing an ideal nidus for DVT during total knee arthroplasty.

t-PA is released from endothelial cells and promotes the formation of plasmin from circulating plasminogen. Plasmin cleaves cross-linked fibrin into fibrin degradation products, which include D-dimer. Plasmin is inactivated by binding to an inhibitor to form α_2-plasmin inhibitor–plasmin complexes (PIP). Similarly, t-PA is inactivated by its inhibitor, plasminogen activator inhibitor (PAI-1), to form t-PA–PAI-1 complexes. t-PA activity represents the net excess of t-PA antigen over inhibitor activity.[20]

During surgery, there is typically enhancement of t-PA activity because of release of t-PA antigen. However, after operation, there is a so-called fibrinolytic shutdown as a result of an increase in PAI-1 release.[21 22] Our results are consistent with this pattern in patients undergoing total knee arthroplasty under both extradural and general anaesthesia. It has been proposed that venous thrombogenesis is more common in patients who have increased PAI-1 concentrations or in patients with suppression of fibrinolysis after operation.[6 23] We found no evidence that the type of anaesthesia influenced fibrinolytic activity in the immediate perioperative period.

It has also been stated that a salutary effect of extradural anaesthesia on fibrinolysis may be caused by concurrent use of adrenaline or ephedrine,[5] as these agents are known to augment t-PA release in young individuals.[24 25] In this study, patients in the extradural anaesthesia group received exogenous adrenaline or ephedrine, or both. In spite of this, no increase in t-PA activity or antigen concentrations was noted in the extradural anaesthesia group. This verifies our previous observation that low-dose adrenaline infusions do not augment t-PA activity in elderly patients during total hip arthroplasty.[26]

Modig and colleagues described more pronounced suppression of fibrinolysis after operation in patients who had general rather than extradural anaesthesia for total hip arthroplasty.[27] Others studying total hip arthroplasty[7 8] or hysterectomy[28] have been unable to repeat this observation. Perhaps the findings of Modig and co-workers could be caused by significant blood loss in their patients who received general anaesthesia (1600 ml),[27] whereas in other studies, intraoperative blood losses were less. In one study which showed no effect of type of anaesthesia on circulating indices of thrombosis and fibrinolysis, eye surgery was studied to eliminate the problem of blood loss and haemodilution.[29] Furthermore, the earlier studies demonstrating enhanced fibrinolysis with extradural anaesthesia used euglobulin lysis time to measure fibrinolytic activity.[27 30] Subsequent studies measuring t-PA activity, t-PA antigen or PIP have shown no differences.[7 8 28 29] Our results further demonstrate that the anaesthetic technique does not affect fibrinolysis when specific assays are used.

Prolongation of extradural analgesia after operation has been advocated as a means of maximizing the potential benefit of extradural anaesthesia on thrombogenesis by either increasing lower extremity blood flow[5 31] or by minimizing postoperative fibrinolytic shutdown.[6] This study did not examine this issue as samples were obtained in the immediate perioperative period. However, retrospective studies have failed to demonstrate any reduction in DVT rate after total knee arthroplasty when using long-acting local anaesthetics (bupivacaine *vs* lignocaine) or when postoperative extradural analgesia is used (compared with i.m. opioids).[32] Ideally, strategies to limit DVT should be initiated before or during surgery[33] as thrombi initially form during operation.[9 34] When thrombi are formed, postoperative therapy can only limit propagation and must rely on intrinsic fibrinolysis to clear them.

This study suggests that the mechanism which results in lower incidences of DVT after total knee arthroplasty using extradural anaesthesia is most likely acting after operation rather than during surgery. Davis and colleagues noted that lower extremity blood flow is increased in the early postoperative period in patients receiving spinal rather than general anaesthesia.[31] Enhanced blood flow may wash out loosely formed thrombi or limit early propagation of existing thrombi. Alternatively, extradural anaesthesia or analgesia may enhance rates of rehabilitation.[35] In the randomized study of 262 patients from which this is a subset, we noted that patients receiving extradural anaesthesia achieved certain rehabilitation milestones earlier than the general anaesthesia group.[4] Perhaps earlier ambulation with extradural anaesthesia reduces DVT by improving deep venous blood flow. In this regard, it is known that mechanical devices such as pneumatic compression stockings[36] or Plexipulse (foot pump),[37] which augment blood flow in the calf, reduce DVT rates after total knee arthroplasty by 40–50%.[36 37]

Acknowledgements

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British Journal of Anaesthesia 1997; **79**: 35–40

Cardioventilatory coupling during anaesthesia

D. C. GALLETLY AND P. D. LARSEN

Summary

In 20 spontaneously breathing patients undergoing minor surgical procedures under general anaesthesia, we examined the timing relationship of heart beat and ventilation. Patients received propofol 2–2.5 mg kg^{-1} and fentanyl 1 μg kg^{-1} and breathed a mixture of 1–1.5% isoflurane and 66% nitrous oxide in oxygen. We recorded ECG R wave times and the start of each inspiration. We observed that: (1) all subjects showed evidence of phase coupling in which heart beats occurred at constant phases of the ventilatory cycle; (2) there was a significant preference for whole number ratios of heart rate to ventilatory frequency; (3) phase coupling was associated frequently with quantal changes in heart rate or ventilatory frequency, or both; (4) six coupling patterns were described according to the timing relationship between the ECG R wave and start of inspiration and according to changes in the number of heart beats within each ventilatory period; (5) phase coupling was achieved primarily by transient changes in ventilatory period. Phase coupling, in concert with respiratory sinus arrhythmia, may optimize the performance of the thoracic pump, matching cardiac filling to venous return. Coupling may therefore have anaesthetic relevance in conditions of impaired cardiac performance or hypovolaemia. (*Br. J. Anaesth.* 1997; **79**: 35–40).

Key words

Heart, heart rate. Ventilation, frequency. Monitoring, electrocardiography. Monitoring, ventilation. Cardiorespiratory system, effects.

Heart rate variability is a consequence of periodic fluctuations in sympathetic and parasympathetic outflow to the heart. Baroreflex inputs to autonomic neurones within the brainstem modulate this efferent activity and, in turn, ventilation modulates the degree to which these baroreceptor inputs influence the firing of autonomic neurones. Respiratory sinus arrhythmia is the result of this ventilatory modulation.

In addition to sinus arrhythmia, heart beats may become "phase coupled" to respiration, such that heart beats occur at constant phases of the respiratory cycle. Although this coupling is poorly seen in alert and active human subjects, it is clearly present during sedation,[1] sleep[2] and in conditions of low cognitive and behavioural activity.[3]

Cardioventilatory coupling in mammals was first described by Walter Coleman in 1921 after experiments performed at the London Zoological Gardens in Regents Park. In one of several classic articles[4 5] he describes how: "The movements of the whiskers of a resting leopard were perfectly regular and indicated its heart rate as 54. The metronome was set at that rate with subdued sound, and expansions of the lungs ceased at strokes of metronome as follows: 5, 5, 5, 6, 5, 5, 5, 6, 5, 5, 5, 6, 3. The animal stirred at 3. This and many other tests indicate that usually with animals at rest and always during sleep the breath begins at multiples of the heart-rate".

In humans, cardiorespiratory synchronization was first described by Galli in 1924.[6] In subsequent years the subject was largely forgotten until, from the 1950s, groups of German physiologists (Hildebrandt, Bucher, Engel, Raschke, Kenner and others)[2 3 6–10] attempted to further define the interaction and determine its mechanism. The subject of cardioventilatory phase coupling is largely confined therefore to German language publications and despite its possible relevance, the anaesthesia literature is devoid of discussion on the subject.

In 1972, Engel, Jaeger and Hildebrandt,[7] using statistical methods, demonstrated the presence of phase coupling in anaesthetized adults and children. Since then advances in computer-based digital signal processing and graphical analysis techniques have made it possible for a more detailed examination of the phenomenon. In this study we sought to further define the frequency and nature of cardioventilatory coupling in patients undergoing surgical procedures under general anaesthesia.

Patients and methods

After obtaining Ethics Committee approval, we studied 20 consenting, unpremedicated ASA I and II adult patients undergoing elective orthopaedic or gynaecological surgery. None was taking regular medications or had evidence of cardiorespiratory disease.

Anaesthesia was induced with propofol 2–2.5 mg kg^{-1} and maintained by spontaneous inhalation of

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D. C GALLETLY, MB, CHB, FRCA, FANZCA, P. D. LARSEN, BSC (HONS), Section of Anaesthesia, Wellington School of Medicine, PO Box 7343, Wellington, New Zealand. Accepted for publication: February 26, 1997.

1–1.5% isoflurane and 66% nitrous oxide in oxygen. After induction, a laryngeal mask was inserted and increments of fentanyl 50–100 μg or morphine 5–10 mg were given as required. In two patients, vecuronium was administered for neuromuscular block and in these, mechanical IPPV was applied to give an end-tidal carbon dioxide partial pressue of 4.7–5.3 kPa. In both patients, spontaneous ventilation recordings were obtained before neuromuscular block.

We monitored arterial oxygen saturation (Sp_{O_2}), end-tidal carbon dioxide concentration, end-tidal isoflurane concentration (Datex AS3), heart rate, ECG (lead CM_5, Corometrics Neo-Trak 502) and timing of inspiration.

Ventilatory timing was measured by incorporating a Ruben non-return valve into the T of the circle absorption system. The valve was modified by addition of a photodetector and light beam across the path of the valve shuttle. This generated a 1.5-V square wave signal while the valve was open (i.e. from start inspiration to end inspiration). Using this system a small delay may be expected from the onset of inspiration until opening of the valve shuttle, however, we considered this delay small in comparison with the duration of a heart period.

For a minimum of 5 min, ECG and photodetector output were recorded continuously using a Macintosh IIcx computer with 16 bit ADC board (National Instruments) and a sampling rate of 500 Hz. Recording of cardioventilatory data began after laryngeal mask insertion and continued until the end of surgery.

ANALYSIS

Analysis of phase coupling was based on the method described by Kenner, Pessenhofer and Schwaberger.[8] From the stored ECG data, we measured the time of each R wave peak and, from the ventilatory signal, we determined the time of each inspiratory onset. From these data, we calculated the interval between each R wave and the following, in addition to the preceding, start of inspiration (RI intervals). RI intervals for each heart beat were then plotted against time of R wave occurrence (RI plot). RI intervals for R waves preceding the inspiration were given a negative subscript and RI intervals after an inspiration were given a positive subscript: RI_{-1} for the beat preceding the inspiration and RI_{+1} , RI_{+2}, etc, for beats after the inspiration

A fixed relationship, or coupling, between heart beats and inspiration is revealed in an RI plot as horizontal banding in which values of $RI_{\pm n}$ maintain relatively constant values over time.

In addition to calculating RI intervals, we determined the degree to which heart rate and ventilatory frequency approached a whole number ratio. We calculated for all time series and for each breath the ratio of heart rate to ventilatory frequency where heart rate was calculated from the median of seven consecutive beats. Integer preference (IP) was defined as a heart rate to ventilatory frequency ratio subtracted from its closest integer value (a ratio of 3.67 becomes 3.67−4=−0.33, a heart rate to ventilatory frequency ratio of 5.01 becomes 5.01−5=0.01). The mean absolute value (|IP|) of this integer preference was calculated for each subject. |IP| values close to 0 indicate an integer ratio.

As a measure of respiratory sinus arrhythmia we took a representative 256-s, artefact-free segment of the RR interval time series. Using previously described methods we performed a fast Fourier analysis on this segment.[11] A measure of ventilatory heart rate modulation was determined by calculating the area under the power spectrum curve between 0.15 and 0.4 Hz.

Statistical analysis was performed only on spontaneously breathing segments in those patients who subsequently underwent artificial ventilation.

All software was purpose written in LabView 2 (National Instruments).

Results

Mean patient age was 39 (range 18–66) yr; 15 were female and mean duration of data recording was 23 (range 6–70) min. Cardioventilatory coupling was observed in all patients. A representative example of data obtained from one subject is shown in figure 1.

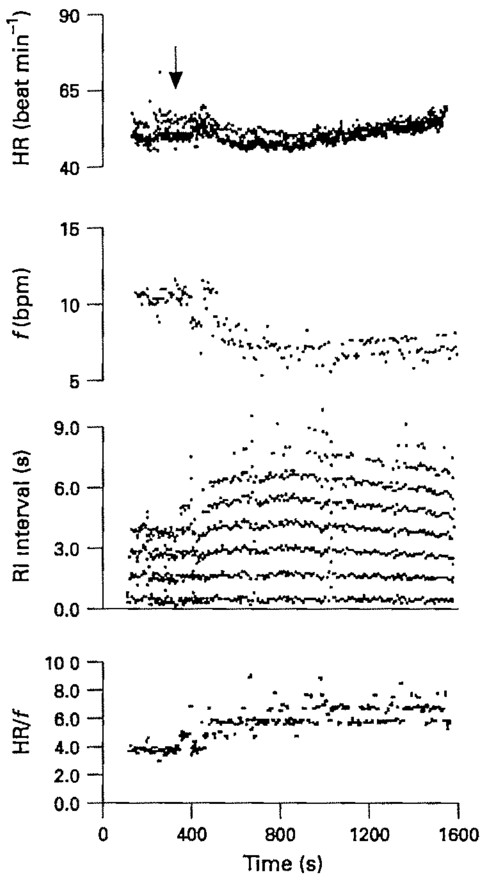

Figure 1 Representative data from one spontaneously breathing patient. Fentanyl 50 μg i.v. was given at 400s (arrow). Beat-to-beat heart rate (HR), breath-to-breath ventilatory frequency (*f*), RI interval and heart rate/ventilatory frequency ratio (HR/*f*) are shown. The RI plot shows horizontal banding indicating cardioventilatory coupling. The increase in number of bands reflects the increasing number of RI intervals per breath as ventilatory frequency decreases after administration of the opioid. Note quantal changes in HR and *f* (shown as banding of their individual time series) and whole number steps in HR/*f* ratio.

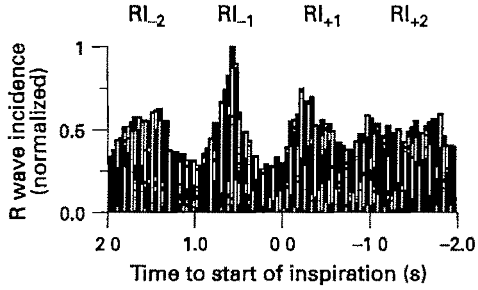

Figure 2 Histogram of R wave occurrence, relative to start of inspiration, normalized and averaged for all subjects.

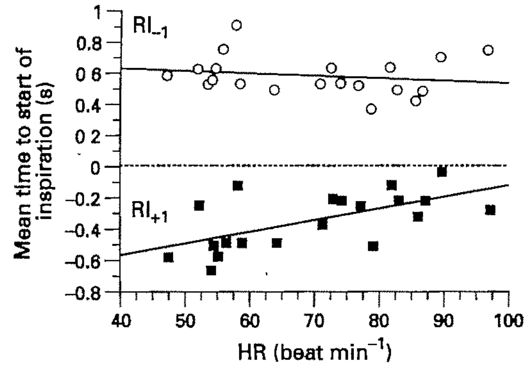

Figure 3 Mean RI$_{-1}$ and RI$_{+1}$ for 20 subjects *vs* mean heart rate (HR). Note the relative constancy of RI$_{-1}$ independent of RR interval (heart rate)

R WAVE ALIGNMENT TO INSPIRATION

Figure 2 is an averaged and normalized histogram of RI intervals for all subjects and shows a peak R wave incidence, corresponding to RI$_{-1}$, at 0.5 s before the start of inspiration. The peak corresponding to RI$_{+1}$ was less apparent as were other R wave alignments. Thus relative to start inspiration, RI$_{-1}$ was the least variable R wave position. Mean RI$_{-1}$ values for all subjects were 0.51 (SD 0.1) s. Mean RI$_{+1}$ inversely correlated with mean heart rate ($P<0.005$) whereas the correlation between mean RI$_{-1}$ and heart rate was not statistically significant (fig. 3).

QUANTAL HEART RATE AND VENTILATORY FREQUENCY ADJUSTMENTS

Both heart rate and ventilatory frequency were observed to fluctuate at times in a quantal manner. This appeared as banding of the beat-to-beat heart rate (or RR interval) and breath-to-breath ventilation rate time series (fig. 1).

Quantal heart rate changes were observed only during periods of cardioventilatory phase coupling. At these times, because R waves occurred at roughly constant intervals after the start of inspiration, RI$_{+1}$ was influenced differently by vagal withdrawal than RI$_{+2}$, RI$_{+3}$, and so on (fig. 4). Thus the RR interval after inspiration was shorter than subsequent intervals giving a banded appearance to the heart rate time series. The width of these bands varied depending on the degree of respiratory sinus arrhythmia.

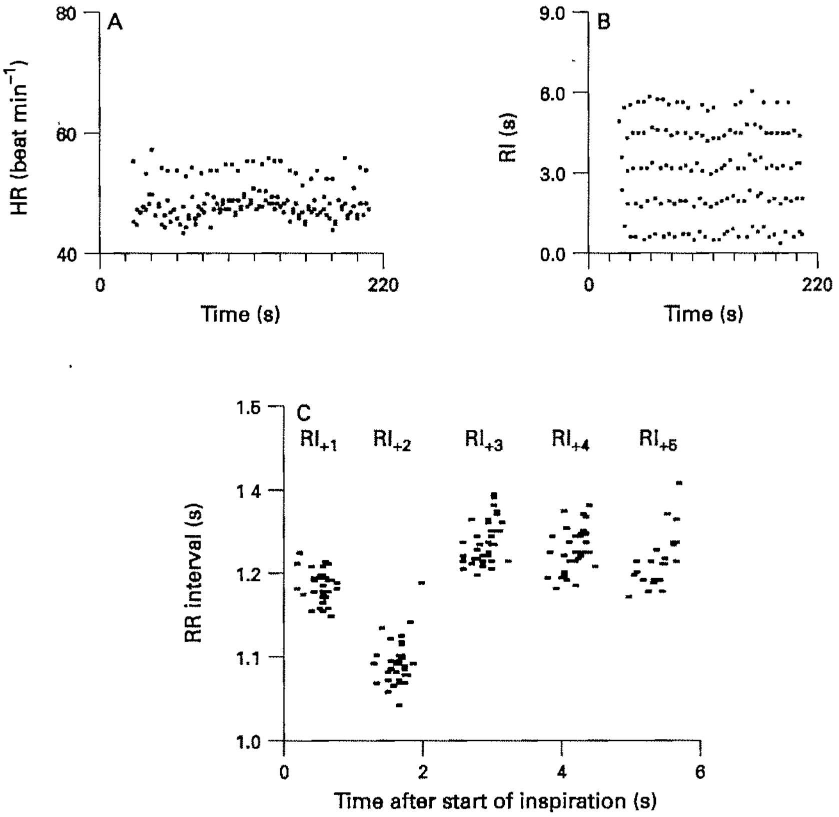

Figure 4 A: Heart rate (HR) time series, B: RI plot and C: RR interval plotted against time after start of inspiration. Note the quantal changes in HR (shown as banding of the HR time series) as a result of the greater degree of vagal withdrawal imposed on RI$_{+1}$ compared with RI$_{+2}$ RI$_{+3}$, RI$_{+4}$ and RI$_{+5}$.

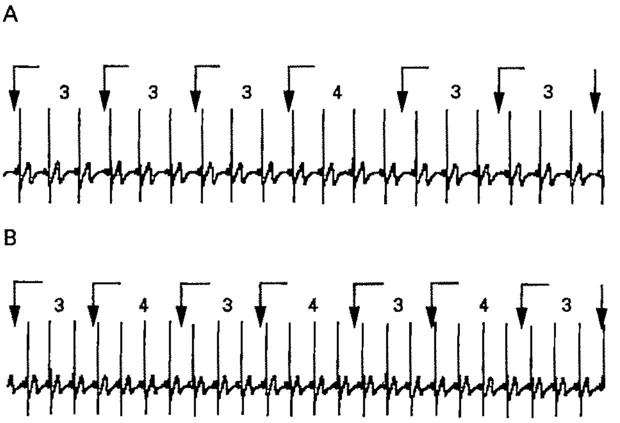

Figure 5 ECG and ventilation in one subject showing; A: a single prolongation in ventilatory period during a synchronized pattern of constant 3:1 ratio coupling; B: alternating 3:1, 4:1 coupling with alternating RI interval, also shown in figure 8D. Arrow indicates start inspiration and horizontal bar the duration of inspiration, numbers refer to heart beats within each ventilatory period.

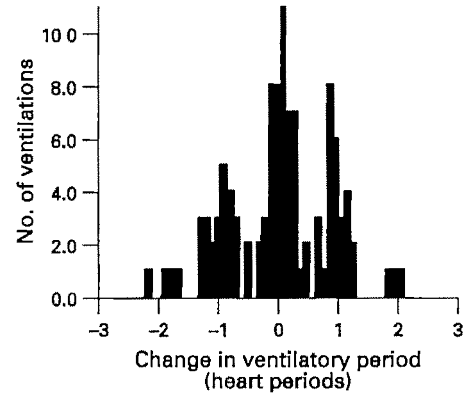

Figure 6 Histogram of breath-to-breath change in ventilatory period as a multiple of the heart period. Data were taken from the subject of figure 1 and show that changes in ventilatory period were frequently in one heart period steps.

Quantal changes were also observed in ventilation. The banded appearance in a ventilation rate time series is seen in figure 1. The quantal change in ventilatory frequency corresponds to transient rate fluctuations as ventilation jumps between different heart rate to ventilatory frequency integer ratios while heart rate is relatively constant. An example is seen in figure 5A where 3:1 coupling is interrupted by a single 4:1 coupling. Because the ventilatory period is extended by approximately one heart period, the observed ventilatory frequency time series banding width (fig. 1) corresponds to approximately one heart period. The histogram in figure 6 shows the distribution of ventilatory periods measured as a multiple of the heart period in one subject and demonstrates the quantal ventilatory adjustments at multiples of the heart period.

INTEGER PREFERENCE

Synchronized coupling, where the heart rate to ventilatory frequency ratio (and number of heart beats within each ventilatory period) remained a constant whole number for periods longer than 60 s, was observed in 50% of subjects. The mean |IP| for all subjects was 0.21 (0.07). This was significantly different ($P<0.05$; Student's t test) from a mean of 0.25 which would be expected if there was no preference for integer or non-integer ratio. Figure 7 shows the histogram of IP values averaged and normalized for all subjects; a clear peak at IP=0 is seen. Rapid transitions between integer ratios are also seen in the heart rate to ventilatory frequency ratio plot of figure 1 and in figure 5.

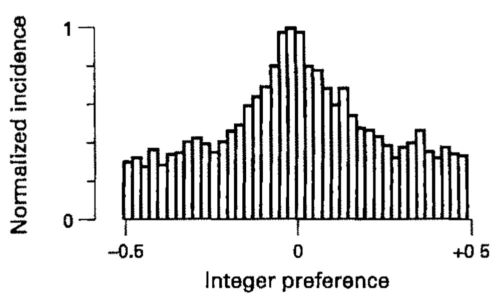

Figure 7 Histogram of integer preference, normalized and averaged for all subjects.

Although we observed the expected diminution of respiratory sinus arrhythmia with age (correlation between area under the ventilatory portion of the RR interval spectrum and age, $P<0.05$), the presence of coupling (RI plots) appeared unaffected and there was no correlation between age and integer preference (mean |IP|).

PATTERNS OF COUPLING

A variety of coupling patterns were observed in the RI plots with subjects commonly showing transition from one to another.

(a) Synchronous coupling (fig. 8A) with constant RI alignments and a strict whole number heart rate to ventilatory frequency ratio. This was observed, for periods longer than 60 s, in 10 (50%) subjects.

(b) Uncoupled with unstructured RI plots (fig. 8B). This was seen in only two (10%) subjects both of whom demonstrated high degrees of respiratory sinus arrhythmia.

(c) Uncoupled with slowly changing RI alignments (fig. 8C). This was observed during periods of intermittent positive pressure ventilation (two of two subjects) and for short periods in six (30%) spontaneously breathing subjects.

(d) Non-synchronous coupling with double banding of the RI plot (fig. 8D). RI intervals for one breath were similar to those two breaths in advance, however consecutive breaths had different RI intervals. Ventilatory period and heart rate to ventilatory frequency ratio alternated between two values. The jumps in ventilatory period were not exactly equal to one heart period, thus RI alignment is slightly different for alternate breaths. This pattern was seen in six subjects (30%). An example is shown in figure 5B.

(e) Coupling with a similar appearance to synchronized coupling but with a varying number of heart beats within each ventilatory period (fig. 8E). This common pattern (100% of subjects) occurred where the heart rate to ventilatory frequency ratio

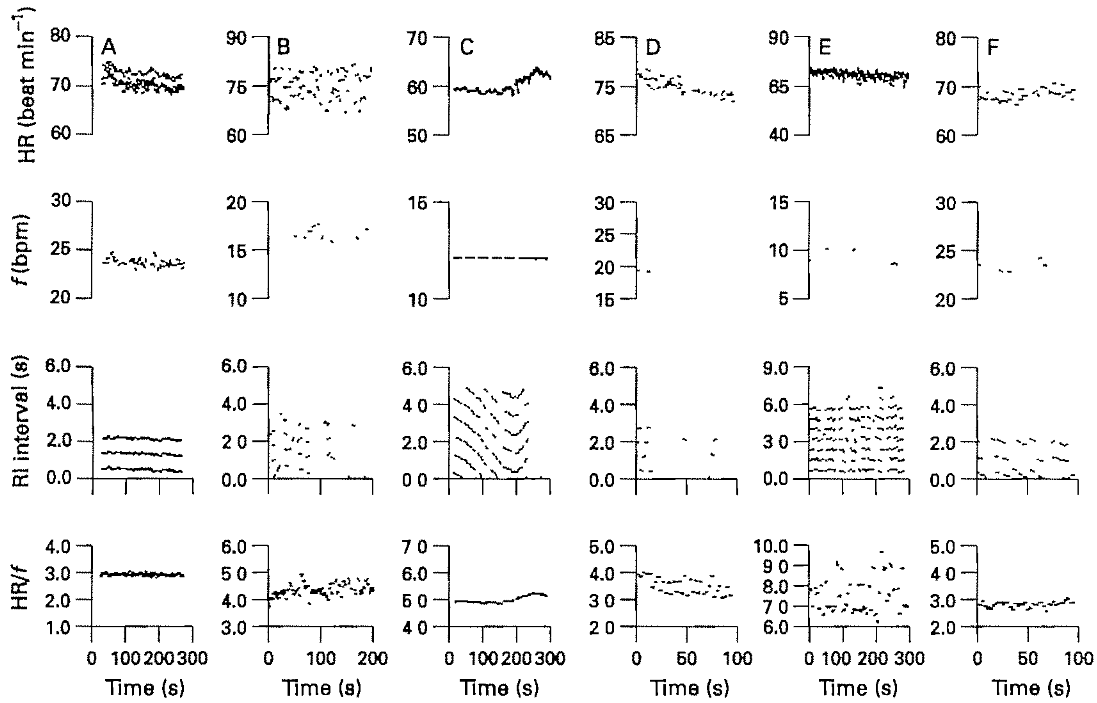

Figure 8 Six observed patterns of cardioventilatory coupling. For each coupling pattern, the figure shows beat-to-beat heart rate (HR), breath-to-breath ventilatory frequency (*f*), RI interval and heart rate/ventilation rate ratio (HR/*f*)

varied but quantal changes in ventilatory period allowed synchronization of R waves to inspiration for each breath.

(f) Non-synchronous coupling with slurring of the RI plot at preferred RI alignments was seen in five (25%) subjects. In figure 8F heart rate and ventilatory frequency are a little out of whole number ratio and RI_{-1} values gradually change away from the preferred 0.5 s. As the RI_{-1} value approaches 0 however, a rapid change in ventilatory periods brings the RI value back to the preferred alignment.

Discussion

In this study we observed cardiorespiratory phase coupling in all of our spontaneously breathing anaesthetized subjects. Although the specific pattern of coupling varied between subjects, and over time, it was rare to observe complete absence.

In order to achieve synchronization of the heart rhythm with ventilation, adjustments to either heart beat timing or ventilation, or both, must occur. We observed that constancy of RI intervals was most pronounced for the R wave immediately preceding inspiration rather than that which follows. RI_{-1} therefore was the most constant RI interval. This suggests that start of inspiration is triggered by an event associated with the preceding heart beat. As fluctuations in RR interval caused by respiratory sinus arrhythmia (fig. 4) occurred only after the start of inspiration, it is likely that these RR fluctuations are of little importance for RI alignment and therefore it is the inspiratory onset itself which is being adjusted to the preceding heart beat. These ventilatory adjustments were seen in our previous study of midazolam sedated patients and in this study (fig. 1) where ventilatory period jumped in a quantal manner to maintain RI alignment despite changing numbers of R waves within each ventilatory period. Kenner, Pessenhofer and Schwaberger[8] noted in rabbits that coupling was achieved by rapid and transient fluctuations in ventilatory frequency and observations of Hinderling,[10] in 1967, that coupling persists in patients with artificial cardiac pacemakers, clearly indicates the importance of modulation of ventilatory period. Quantal ventilatory frequency changes were first noted in anaesthesia by Goodman,[12 13] who ascribed the phenomena to a central multifrequency oscillator.

Afferent cardiovascular input which triggers phase shifts in ventilatory timing are not known with certainty. In experimental animals, coupling is abolished by vagotomy[8] and deafferentation of vagal fibres from the right atrium[14] and persists in the presence of artificial cardiac pacing and artificially induced pulsatile carotid flow.[9] Thus, afferent baroreceptor or atrial stretch receptor information, or both, is probably important in mediating phase coupling.

Control of cardioventilatory timing is thus a balance between respiratory sinus arrhythmia, achieved through heart rate adjustment, and phase coupling achieved through ventilatory adjustment. The relative importance of each however may vary depending on the subject and condition. It is known that with increasing age, respiratory sinus arrhythmia diminishes, whereas we observed no effect of age on coupling or integer preference. In contrast, sinus arrhythmia persists at all levels of cognitive arousal, whereas phase coupling is seen best during relaxation, sleep and anaesthesia.

It is traditionally believed that the increase in heart rate during inspiration (respiratory sinus arrhythmia) is of practical importance. As the negative intrathoracic pressure of inspiration causes increased venous return, vagolysis during the inspiratory period augments the performance of this "thoracic pump" and, with the Starling mechanism, helps match cardiac output to venous return. It is possible that cardioventilatory phase coupling may optimize the thoracic pump further. The R wave occurs approximately 0.5 s before the onset of inspiratory airflow. At inspiration therefore, ventricular ejection has occurred and the AV valves are opening, allowing rapid ventricular filling. In the presence of phase coupling, ventricular filling occurs at the same time that venous return is increasing as a result of negative intrathoracic pressure. Because of vagal withdrawal caused by respiratory sinus arrhythmia, a shortened RR interval occurs for the next heart beat allowing further filling and ejection of the heart during the inspiratory period. Thus phase coupling, in concert with sinus arrhythmia and the Starling mechanism, may optimize matching of venous return and cardiac filling.

In summary, respiratory sinus arrhythmia and cardioventilatory phase coupling together contribute to the timing of breathing and heart beats during anaesthesia. The phenomenon is readily apparent to the anaesthetist if excursions of the breathing bag and ECG tone are compared in spontaneously breathing patients. Observation of this link between breathing and heart beats clearly indicates the intimate relationship between cardiac and ventilatory dynamics.

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Effect of domperidone on the ventilatory response to transient hyperoxia in patients anaesthetized with isoflurane

I. T. FOO, P. M. WARREN AND G. B. DRUMMOND

Summary

We have studied the ventilatory responses to transient hyperoxia in two groups of patients (n=10) anaesthetized with isoflurane (0.3 MAC); patients were allocated randomly to receive either domperidone or placebo orally before anaesthesia. In each patient, five two-breath oxygen tests were averaged and minute ventilation ($\dot{V}\text{E}^{\text{inst}}$) or mean inspiratory flow rate ($V\text{T}/T\text{I}$) for each post-test breath was compared with the mean values for these variables during baseline ventilation. A decrease to less than the 95% confidence limits of mean baseline values was considered a definite response. According to this definition, transient hyperoxia decreased $\dot{V}\text{E}^{\text{inst}}$ in nine of 10 patients in the placebo group and in all patients in the domperidone group. Similar changes occurred in $V\text{T}/T\text{I}$, with eight of 10 definite responses in the placebo group and 10 of 10 in the domperidone group. Compared with placebo, in the domperidone group there were larger changes in $\dot{V}\text{E}^{\text{inst}}$ (0.30 *vs* 0.55 litre min^{-1} (P=0.05)) and $V\text{T}/T\text{I}$ (8.5 *vs* 26.6 ml s^{-1} (P=0.02)) from respective baselines. Peripheral chemoreceptors appeared to be active during isoflurane anaesthesia and domperidone pretreatment enhanced this activity by increasing respiratory drive. (*Br. J. Anaesth.* 1997; **79**: 41–46).

Key words
Anaesthetics volatile, isoflurane. Pharmacology, domperidone. Reflexes, chemoreceptors. Ventilation, spontaneous. Ventilation, hypoxic response.

Knill and co-workers have shown that the ventilatory response to hypoxia (HVR) in humans is easily depressed by volatile anaesthetics.[1–3] Anaesthetic concentrations of halothane, enflurane and isoflurane virtually abolished HVR and even subanaesthetic concentrations of these agents reduced the response considerably. However, recent studies have shown that HVR is not as sensitive to isoflurane and ventilatory response to hypoxia remained in patients anaesthetized with 0.6–1.1 MAC of isoflurane.[4–6] Animal studies also provide conflicting data as to whether or not HVR is depressed by volatile anaesthetics.[7 8]

The site of action of volatile agents on HVR remains unclear. Limited studies in humans suggest that the carotid bodies are the most likely site of action.[9–11] However, the peripheral chemosensors appear to be active during light halothane anaesthesia. Clergue and co-workers[12] used a method derived from Dejours' test to assess the response to hypoxia from the transient decrease in ventilation after oxygen was substituted for room air, where the time course of response indicates a rapid (peripheral) reflex.

We have assessed if peripheral chemoreceptors are active during isoflurane anaesthesia by observing ventilatory responses to transient hyperoxia during light isoflurane anaesthesia. This test, derived from Dejours' test, is based on the concept that the initial response to hyperoxia (transient ventilatory depression) is mediated by peripheral chemoreceptors which respond more promptly, and that this effect occurs before the onset of secondary responses. The second aim of this study was to see if domperidone, a selective dopamine D_2 receptor antagonist which does not cross the blood–brain barrier,[13] could augment the response to this test in patients anaesthetized with isoflurane. We showed in a previous study[14] that domperidone offset the suppressive effect of isoflurane on HVR, presumably by antagonism of dopamine D_2 receptors in the carotid bodies.

Patients and methods

This double-blind, placebo-controlled study was approved by the local Research Ethics Committee. Written informed consent was obtained from 20 patients who were ASA I, not overweight and aged 18–65 yr. Patients were allocated randomly to receive either domperidone 20 mg or placebo tablets 1 h before arrival in the anaesthetic room.

In the anaesthetic room, an i.v. infusion was commenced and non-invasive monitoring of arterial pressure, ECG and pulse oximetry started. General

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IRWIN T. FOO*, BSC(HONS), MB, BCHIR, MRCP(UK), FRCA, GORDON B. DRUMMOND, MA, MB, CHB, FRCA, Department of Anaesthetics, University of Edinburgh, Edinburgh. PATRICIA M. WARREN, BSC, PHD, Rayne Laboratory, Unit of Respiratory Medicine, Department of Medicine, Royal Infirmary, Edinburgh.
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*Address for correspondence: Department of Anaesthetics, Royal Infirmary of Edinburgh, Lauriston Place, Edinburgh EH3 9YW.

anaesthesia was induced with etomidate 0.3 mg kg^{-1} i.v. and anaesthesia was deepened with isoflurane and nitrous oxide in oxygen, with the patient breathing spontaneously. When anaesthesia was judged to be of adequate depth for tracheal intubation, laryngoscopy was performed and the larynx sprayed with a metered dose of a lignocaine preparation (Xylocaine, Astra Pharmaceuticals) using no more than 40 mg. After a short delay, the trachea was intubated and the inspired oxygen concentration was reduced to and maintained at 20% for the duration of the study. At the same time, the inspired isoflurane concentration was adjusted to obtain a stable end-tidal concentration of 0.4%, as measured by a Brüel and Kjaer gas monitor 1304, sampling at 90 ml min^{-1}, with a response time of less than 360 ms.[15] Headphones were placed on the patient's ears and white noise was played to prevent noise affecting breathing, and the arterial pressure cuff was not automatically inflated routinely in case it altered breathing pattern. Measurements of ventilatory variables during anaesthesia were started after a stable end-tidal isoflurane concentration had been present for at least 20 min.

The tracheal tube was connected via a screen pneumotachograph (F100L, Mercury Electronics) to an Ambu Hesse non-rebreathing valve. The pneumotachograph pressure signal was measured with a Furness FC044 differential pressure transducer (±10 mm H_2O). The inspiratory side of the valve was connected to a large bore two-way tap which allowed rapid changes between two supply systems. Anaesthetic gases (20% oxygen, isoflurane and nitrous oxide) were provided from a 4-litre reservoir bag fitted with a spill valve to reduce positive pressure in the supply tubing. Oxygen was supplied (flow rate of 6 litre min^{-1}) from a T-piece system using a 1-m length of anaesthetic tubing as a reservoir. The deadspace of the breathing system was approximately 80 ml.

Inspired and expired carbon dioxide and oxygen partial pressures and inspired and expired concentrations of isoflurane were measured continuously by the Brüel and Kjaer gas monitor. Gas monitor and flow signals were recorded on a lap-top computer using the commercial respiratory monitoring software Cardas (version 2.07 advanced, Oxcams, Oxford), running in MS-DOS (version 6.2) for later off-line analysis. The flow signal was integrated to obtain values for tidal volume (V_T) and instantaneous minute ventilation ($\dot{V}_E^{inst}$) calculated from tidal volume and respiratory cycle duration. Before each study, the pneumotachograph was calibrated against a 1-litre calibration syringe and the gas monitor was calibrated using a reference gas.

When clinically stable anaesthesia was achieved, the tap was turned during expiration so that two breaths of 100% oxygen were given. Tests were repeated at 2-min intervals. Five satisfactory two-breath oxygen tests were recorded. At the end of the testing sequence, a venous blood sample was obtained for measurement of plasma concentrations of domperidone and surgery started.

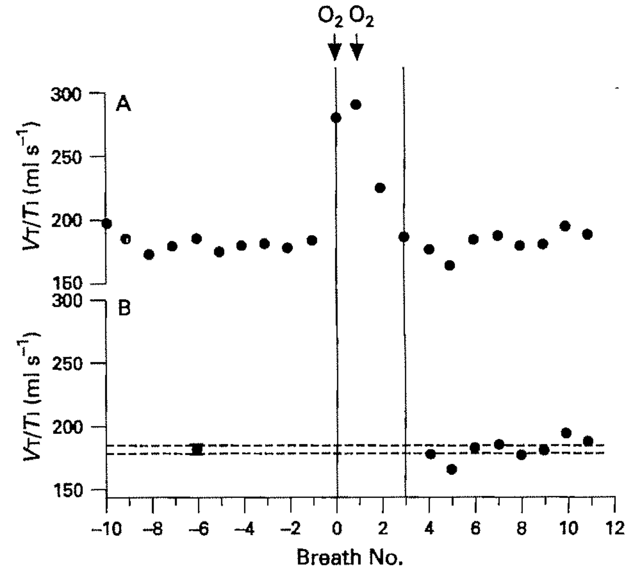

Figure 1 A: Mean inspiratory flow rate (V_T/T_I) from one patient showing the 10 breaths used as baseline and the post-test breaths analysed. The vertical lines indicate the two oxygen test breaths and the two breaths omitted from the analysis. B: Method used for analysis of transients. Baseline mean and 95% confidence limits (CL) used for testing against each post-test breath. Breaths below the horizontal dashed line are below the 95% CL of baseline and were considered definite responses (see text for further explanation)

ANALYSIS AND STATISTICS

We measured the 10 breaths before the two hyperoxic breaths as baseline. We ignored the two hyperoxic breaths (test breaths) and the following two breaths, as it required these additional breaths to elapse for exhaled oxygen to return to pre-test values. We then measured the eight subsequent breaths (fig. 1). Previous work has shown that maximum change in ventilation occurs after six breaths from the change in inspired oxygen.[11]

To reduce the influence of normal variation in breathing, the five hyperoxic tests for each patient were averaged on a breath-by-breath basis. We calculated means and 95% confidence limits (CL) for $\dot{V}_E^{inst}$ and mean inspiratory flow rate (V_T/T_I) for the 10 breaths used as baseline, and inspected the post-test breaths for a reduction to less than 95% CL of baseline. If any post-test breath was reduced below the 95% CL of baseline, this was considered a definite response provided that breaths increased again towards baseline after reaching a minimum value (fig. 1). From the V_T/T_I results, we recorded the post-test breath number with the smallest V_T/T_I. This breath was used subsequently for analysis of frequency, and inspiratory and expiratory time changes from baseline. The time from the hyperoxic stimulus to the breath with the smallest V_T/T_I was also noted.

To assess the reliability and consistency of this method of analysis, a random selection of five sets of 22 breaths was obtained in each patient during baseline breathing and subjected to the same averaging and analysis to assess if similar results could be obtained without the hyperoxic test breaths. Definite responses for both the placebo and domperidone groups were compared for any significant difference using the chi-square test with Yates' correction.

To assess if domperidone augmented the response to the hyperoxic test breaths, the mean maximal reductions in $\dot{V}_E^{inst}$ and V_T/T_I from baseline was calculated for both the placebo and domperidone groups. These values, and T_I and T_E changes from baseline, based on the minimum V_T/T_I post-test breath, were compared between groups using the Mann–Whitney test. Statistical significance was set at the 5% level.

Results

All patients completed the study without complications. The placebo and domperidone groups were comparable in age (mean 33 (range 26–53) and 34 (22–56) yr, respectively), weight (mean 73 (SD 15) and 72 (15) kg, respectively) and sex distribution (5M, 5F and 6M, 4F, respectively). Mean oxygen saturations were 92.7 (SD 2.3) % and 93.3 (1.9) %, respectively, and no patient had an oxygen saturation less than 90% when breathing an inspired oxygen concentration of 20%. Mean baseline end-tidal carbon dioxide partial pressures before the oxygen tests were 5.5 (range 4.5–6.0) kPa for the placebo group and 5.3 (4.2–6.3) kPa for the domperidone groups (ns).

After oxygen, all patients showed a transient reduction in $\dot{V}_E^{inst}$ and V_T/T_I with recovery towards baseline values by the end of the analysis period. $\dot{V}_E^{inst}$ and V_T/T_I analysis showed that the post-test breath with the maximum reduction occurred consistently within the same breath or two for each patient. In three patients, there were two consecutive transient reductions in $\dot{V}_E^{inst}$ and V_T/T_I and in these cases, the first transient was used for analysis.

Considering $\dot{V}_E^{inst}$, nine of 10 patients who received placebo and 10 of 10 patients who received domperidone demonstrated definite responses to the test. When the analysis was repeated for V_T/T_I, there were eight definite responses in the placebo group and 10 in the domperidone group. There was no significant difference in response frequency between groups. For both placebo and domperidone groups, mean times to minimum V_T/T_I after two hyperoxic breaths were 13.5 (SD 2.0) s and 14.9 (2.6) s, respectively. This corresponded to the minimum V_T/T_I breath occurring between breaths 5 and 11. This appeared to depend on the ventilatory frequency of the individual patient when the testing was performed, with higher ventilatory frequencies associated with a larger number of breaths to the minimum. Randomly selected sequences of breaths in each patient subjected to the same analysis did not show any transient reduction in minute ventilation with recovery towards baseline values.

Mean baseline $\dot{V}_E^{inst}$ and minimum minute ventilation after the test for each patient in each group are shown in table 1. The magnitude of the post-test reduction ranged from 0.04 to 0.53 litre min^{-1} of mean baseline ventilation in the placebo group and from 0.21 to 1.74 litre min^{-1} in the domperidone group. The overall mean reduction in ventilation was 0.30 litre min^{-1} for the placebo group and 0.55 litre min^{-1} for the domperidone group (table 2). These reductions differed significantly (P=0.05).

Mean baseline V_T/T_I and minimum V_T/T_I after the test for each patient in each group are shown in table 1. Changes in V_T/T_I after the test varied from an increase of 1 ml s^{-1} to a decrease of 27 ml s^{-1} compared with mean baseline values (placebo) and

Table 1 Mean (95% confidence limits) baseline $\dot{V}_E$, V_T/T_I, T_I and T_E, and post-test values after averaging of the five hyperoxic tests for each patient in the placebo and domperidone groups. Post-test $\dot{V}_E$ and V_T/T_I, are minimum values and *indicates definite response, that is outside the 95% confidence limit of baseline $\dot{V}_E$, and V_T/T_I, respectively. Post-test T_I and T_E, values were derived from the minimum post-test V_T/T_I, breath number

Patient No.	Baseline $\dot{V}_E$ (litre min^{-1})	$\dot{V}_E$ Minimum post-test (litre min^{-1})	Baseline V_T/T_I, (ml s^{-1})	V_T/T_I minimum post-test (ml s^{-1})	Baseline T_I (s)	Post-test T_I (s)	Baseline T_E (s)	Post-test T_E (s)
Placebo group								
1	5.88 (5.81, 5.95)	5.84	222 (217, 227)	219	1.17 (1.14, 1.21)	1.15	1.48 (1.46, 1.50)	1.37
2	7.76 (7.70, 7.82)	7.34*	295 (290, 300)	288*	1.00 (0.98, 1.02)	1.05	1.27 (1.25, 1.29)	1.27
3	6.86 (6.80, 6.92)	6.33*	264 (260, 268)	237*	0.97 (0.95, 0.99)	1.05	1.26 (1.23, 1.29)	1.30
4	6.76 (6.71, 6.81)	6.25*	253 (250, 256)	236*	0.95 (0.94, 0.97)	1.08	1.18 (1.16, 1.20)	1.36
9	4.82 (4.78, 4.86)	4.64*	184 (181, 186)	176*	1.11 (1.10, 1.13)	1.17	1.43 (1.41, 1.45)	1.48
11	5.01 (4.96, 5.06)	4.74*	183 (181, 185)	177*	0.89 (0.88, 0.90)	0.91	1.06 (1.04, 1.08)	1.14
14	6.45 (6.36, 6.54)	6.24*	235 (232, 239)	237	1.26 (1.24, 1.28)	1.23	1.49 (1.46, 1.52)	1.57
16	5.37 (5.31, 5.43)	4.99*	207 (205, 209)	199*	1.12 (1.11, 1.14)	1.14	1.42 (1.40, 1.44)	1.59
17	4.72 (4.67, 4.77)	4.58*	188 (186, 189)	183*	1.00 (0.98, 1.01)	1.02	1.39 (1.37, 1.41)	1.39
18	5.88 (5.82, 5.94)	5.59*	203 (201, 206)	196*	0.89 (0.87, 0.91)	0.94	0.94 (0.92, 0.96)	1.05
Domperidone group								
6	6.82 (6.72, 6.92)	6.28*	241 (233, 248)	219*	1.30 (1.25, 1.35)	1.47	1.44 (1.38, 1.50)	1.56
7	5.43 (5.33, 5.53)	5.12*	210 (206, 214)	197*	1.39 (1.37, 1.42)	1.47	1.84 (1.81, 1.87)	1.91
8	7.66 (7.50, 7.82)	7.17*	272 (263, 280)	252*	1.26 (1.21, 1.31)	1.35	1.40 (1.37, 1.43)	1.47
10	6.11 (6.03, 6.19)	5.65*	226 (220, 231)	191*	1.11 (1.08, 1.14)	1.34	1.32 (1.28, 1.36)	1.41
12	8.66 (8.54, 8.78)	6.92*	372 (365, 378)	296*	1.07 (1.05, 1.09)	1.24	1.67 (1.64, 1.69)	1.75
13	7.17 (7.00, 7.34)	6.56*	266 (255, 277)	229*	1.10 (1.05, 1.15)	1.25	1.31 (1.26, 1.36)	1.33
15	5.73 (5.66, 5.80)	5.45*	188 (187, 190)	183*	0.93 (0.92, 0.94)	0.99	0.90 (0.89, 0.91)	0.97
19	5.76 (5.71, 5.81)	5.55*	206 (204, 209)	200*	0.90 (0.89, 0.91)	0.92	1.03 (1.01, 1.05)	1.07
21	6.52 (6.44, 6.60)	6.10*	290 (281, 300)	251*	1.12 (1.07, 1.17)	1.29	1.42 (1.39, 1.45)	1.40
22	6.81 (6.59, 7.03)	6.39*	240 (238, 242)	228*	0.64 (0.63, 0.65)	0.65	0.72 (0.71, 0.73)	0.74

Table 2 Mean (range) baseline $\dot{V}_E$, V_T/T_I, T_I and T_E, and post-test values for the placebo and domperidone groups. Post-test $\dot{V}_E$ and V_T/T_I are minimum values and post-test T_I and T_E values were derived from the minimum post-test V_T/T_I breath number. Magnitude of change between baseline and post-test values are shown and *indicates significant difference ($P \leq 0.05$) from placebo

	Baseline	Minimum post-test	Δ Baseline— minimum post-test
$\dot{V}_E$ (litre min^{-1})			
Placebo	5.96 (4.72, 7.76)	5.65 (4.58, 7.34)	0.30 (0.04, 0.53)
Domperidone	6.67 (5.43, 8.66)	6.12 (5.12, 6.92)	0.55 (0.21, 1.74)*
V_T/T_I (ml s^{-1})			
Placebo	223 (183, 295)	215 (176, 288)	9 (−1, 27)
Domperidone	251 (188, 372)	224 (183, 296)	27 (6, 76)*
	Baseline	Post-test	Δ Baseline—post-test
T_I (s)			
Placebo	1 04 (0.89, 1.26)	1.07 (0.91, 1.23)	−0.04 (−0.13, 0.03)
Domperidone	1.08 (0.64, 1.39)	1.20 (0.65, 1.47)	−0.12 (−0.23, −0.01)*
T_E (s)			
Placebo	1.29 (0.94, 1.49)	1.35 (1.05, 1.59)	−0.06 (−0.18, 0.11)
Domperidone	1.31 (0.72, 1.84)	1.36 (0.74, 1.91)	−0.06 (−0.12, 0.02)

decreases from 6 to 76 ml s^{-1} (domperidone). The mean change was −9 ml s^{-1} for the placebo group and −27 ml s^{-1} for the domperidone group (table 2). These changes were statistically significantly ($P=0.02$).

Timing variables (T_I and T_E) for the minimum post-test V_T/T_I breath were compared with respective mean baseline values. With the exception of data from two patients in the placebo group, inspiratory times were lengthened after the test in both groups compared with baseline values (table 1). The mean increase in inspiration time for the placebo group was 0.04 s and 0.12 s for the domperidone group (table 2). There was a significant difference between groups ($P=0.02$). Expiration times were more variable but the trend was towards increasing expiration time in both groups (table 1). The mean increase for both groups was 0.06 s (table 2).

Mean plasma concentration of domperidone in the domperidone group was 7.9 (range 2.0–19.3) ng ml^{-1}. There was no correlation between plasma concentrations of domperidone and the size of the transient reductions in $\dot{V}_E^{inst}$ or V_T/T_I.

Discussion

We have shown that peripheral chemoreceptor activity was present in a majority of patients during isoflurane anaesthesia. Pre-existing stimulus to breathing was shown by transient depression of both $\dot{V}_E^{inst}$ and V_T/T_I after two breaths of 100% oxygen. With domperidone pretreatment, patients showed greater reductions in both $\dot{V}_E^{inst}$ and V_T/T_I after two breaths of 100% oxygen.

We reduced the respiratory depressant effects of other anaesthetic agents in this study by using etomidate for induction of anaesthesia, which has a short duration of action, and by avoiding the use of opioids. We averaged the repeated tests in each individual to reduce breath-to-breath variability so that small changes in ventilatory variables (as produced by this transient hyperoxia test) were more likely to be detected. Our method of testing for a definite response to hyperoxia is similar to that used in human studies involving single-breath carbon dioxide tests of peripheral chemosensitivity.[16] Randomly selected breaths subjected to the same analysis did not demonstrate the clear pattern of reduction followed by recovery towards baseline and we believe that this method of analysis reliably detected transient changes in responses. In our analysis, we ignored the two hyperoxic breaths (test breaths) and the following two breaths as there was a delay for the expired oxygen to return to baseline and we did not correct the pneumotachograph for changes in gas composition. As previous work showed that the maximum change occurred six breaths after the change in inspired oxygen,[11] we were unlikely to have missed the maximum change.

We used a variation of Dejours' test to assess the activity of the peripheral chemoreceptors during isoflurane anaesthesia. With this technique in resting awake humans, the magnitude of ventilatory change is approximately 8–10% of pre-stimulus baseline ventilation and occurs approximately 10 s after the stimulus.[17] In our study, during isoflurane anaesthesia, mean ventilatory change was 4.9% in the placebo group and 7.7% in the domperidone group and mean time to minimum V_T/T_I after stimulus was 13.5 s in the placebo group and 14.9 s in the domperidone group. This is longer than in awake subjects. Washin of oxygen to the alveoli and hence the change in arterial oxygen content may take longer during anaesthesia because ventilation is less in the anaesthetized subject. Alternatively, control of ventilation may be different from the awake state.

There are possible drawbacks of this test to assess chemoreceptor activity during anaesthesia. Hyperoxia can increase blood Pa_{CO_2} via the Haldane effect and thereby cause an increase in ventilation. Furthermore, hyperoxia can reduce cerebral blood flow which would tend to increase brain P_{CO_2} and thus also ventilation.[18] These effects, which are probably less rapid than effects at the peripheral chemoreceptors, would tend to oppose the decrease in ventilation caused by hyperoxia and therefore underestimate the magnitude of the ventilatory output of the peripheral chemoreceptors.

Duffin, Triscott and Whitwam[11] studied patients after opioid premedication and found that 0.7–0.8% halothane in air substantially decreased the ventilatory response to two breaths of oxygen compared with the response during thiopentone anaesthesia.

They concluded that halothane reduced the activity and responsiveness of peripheral chemoreceptors. As we did not have a group of patients in this study who did not receive isoflurane, we were unable to determine the effect of isoflurane anaesthesia *per se.* Our results only indicate that peripheral chemoreceptors appeared to be active during isoflurane anaesthesia. Different anaesthetic techniques such as the use of opioids and nitrous oxide and different ways of analysing the breaths may account for some of the differences observed. Furthermore, the anaesthetic concentrations used were different in the two studies; Duffin, Triscott and Whitwam[11] used approximately 1 MAC of halothane while we used approximately 0.3 MAC of isoflurane and 80% nitrous oxide. This difference could have influenced the degree of suppression of the peripheral chemoreceptors by these volatile agents. Nevertheless, it is likely that in our patients with an end-tidal isoflurane concentration of 0.4% (approximately 0.3 MAC), peripheral chemoreceptor activity was still present and responsive to changes in oxygen tensions, but perhaps not as vigorously as in awake subjects. Others have studied patients anaesthetized with 1.5% halothane, using a method derived from Dejours' test, and found that peripheral chemoreceptor activity was depressed but not abolished.[12]

Knill and coworkers[3] found that even at 0.1 MAC of isoflurane, there was a 50% reduction in the ventilatory response to isocapnic hypoxia. This was confirmed recently by van den Elsen and colleagues[10] who extended the concentration of isoflurane to 0.2 MAC and found a 65% reduction in isocapnic HVR. At anaesthetic concentrations of 1.1 MAC, HVR was virtually abolished.[3] This suggested that HVR and therefore the peripheral chemoreflex pathway was highly sensitive to the effects of isoflurane. However, our results and those of Clergue and co-workers[12] suggest that peripheral chemoreceptors are not "silent" at anaesthetic concentrations of isoflurane and halothane, respectively, suggesting that although peripheral chemoreceptor responses are depressed, this is perhaps not to the degree as suggested by previous investigators.[3] Our findings also support recent studies by Lindahl's group[4–6] who found persistent ventilatory responses to hypoxia under poikilocapnic conditions in patients anaesthetized with 0.6–0.85 MAC of isoflurane and a reduction of 60–70% in HVR under isocapnic conditions with 0.85–1.1 MAC of isoflurane. Therefore, anaesthetic concentrations of isoflurane do not appear to suppress HVR to the same extent as that found by previous investigators.[3 10] Differences in experimental conditions may account for some of these differences.[10]

Washin studies of subanaesthetic halothane and isoflurane[9 10] suggest that the most likely site of action of volatile agents is at the peripheral chemoreceptors. Depression of hypoxaemic-driven ventilation by halothane and isoflurane occurred extremely rapidly, within the first minute of inhalation. For isoflurane, it was estimated that after 30 s of isoflurane inhalation, the carotid body isoflurane tension would be approximately 90% of end-tidal, whereas the brain isoflurane tension would be approximately 8% of end-tidal.[10] Therefore, ventilatory depression occurring within 30 s of isoflurane inhalation is best explained by an action of isoflurane at the peripheral chemoreceptors. However, Whitwam and co-workers[19] demonstrated in anaesthetized patients that there was a mean delay of only 10 s in central chemoreceptor ventilatory response to i.v. injection of sodium bicarbonate (causing an increase in Pa_{CO_2}) when peripheral chemoreceptor activity was depressed by hyperoxia. This suggests that the time lag between the effect of isoflurane at central and peripheral chemoreceptor sites during washin could also be in the region of 10 s. Therefore, a central effect of subanaesthetic isoflurane cannot be excluded in the first 30 s of isoflurane washin and overall suppression of HVR at anaesthetic doses could be caused by a combination of peripheral and central effects.

The second aim of this study was to determine if domperidone, a selective dopamine D_2 receptor antagonist which does not readily cross the blood–brain barrier,[13] could augment the response to transient hyperoxia in patients anaesthetized with isoflurane. Domperidone augments HVR in humans[20] and can offset the suppression caused by isoflurane on the ventilatory response to hypoxia.[14] We found that with domperidone pretreatment, all patients showed positive results to transient hyperoxia suggesting that with increased ventilatory drive, it was easier to demonstrate the transient reductions in both $\dot{V}\mathrm{E}^{\mathrm{inst}}$ and $V\mathrm{T}/T\mathrm{I}$ after two breaths of 100% oxygen.

Analysis using $V\mathrm{T}/T\mathrm{I}$ instead of breath-by-breath minute ventilation demonstrated a greater difference between placebo and domperidone. $V\mathrm{T}/T\mathrm{I}$ is a measure of respiratory drive allowing minute ventilation to be separated into drive and timing components: $\dot{V}\mathrm{E}^{\mathrm{inst}}$ is the product of $V\mathrm{T}/T\mathrm{I}$ and $T\mathrm{I}/T\mathrm{TOT}$ (timing component where $T\mathrm{TOT}$ is the sum of $T\mathrm{I}$ and $T\mathrm{E}$).[21] When inspiratory and expiratory times were compared between groups, only $T\mathrm{I}$ was significantly different, with domperidone causing an increase in inspiration time. These results support the observations of Clergue and co-workers who found a prompt change in $T\mathrm{I}$ after oxygen breathing commenced.[12]

In summary, our data support the view that peripheral chemoreceptors remain active during isoflurane anaesthesia. Their function may be depressed by isoflurane, but perhaps not as much as suggested previously. Domperidone enhanced peripheral chemosensor activity by increasing respiratory drive during isoflurane anaesthesia.

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Accuracy and clinical performance of a continuous intra-arterial blood-gas monitoring system during thoracoscopic surgery†

A. Zollinger, D. R. Spahn, T. Singer, M. P. Zalunardo, S. Stoehr, W. Weder and T. Pasch

Summary

Accuracy and performance of the only currently available intra-arterial blood-gas monitoring system (Paratrend 7, PT7) were assessed in 23 patients during thoracoscopic surgery using one-lung ventilation. Over a wide range of values for arterial P_{O_2} (6.1–61.1 kPa), P_{CO_2} (4.1–9.5 kPa) and pH (7.19–7.50), 138 arterial blood-gas values obtained by PT7 were compared with corresponding *in vitro* laboratory blood-gas measurements. We found good clinical performance with the PT7 and good agreement between PT7 values and *in vitro* measurements for arterial P_{O_2} (bias (1.96 SD)=0.38 (9.52) kPa), P_{CO_2} (0.31 (0.76) kPa) and pH (−0.017 (0.065)). Also, the bias for sequential changes between two consecutive times was not significantly different from the ideal value of 0. We conclude that the PT7 is helpful in monitoring patients during thoracoscopy. (*Br. J. Anaesth.* 1997; **79**: 47–52).

Key words
Measurement techniques, gas exchange. Equipment, blood-gas monitors. Surgery, thoracic. Ventilation, one-lung.

Video-assisted thoracoscopic surgery is used widely for an increasing number of diagnostic and therapeutic procedures in patients with compromised lung function. Additionally, one-lung ventilation (OLV) is necessary to provide a collapsed lung on the side of operation, and this is often associated with significant changes in arterial blood-gas tensions. Oxygenation may be impaired by significant intrapulmonary shunting, and carbon dioxide removal may be impaired by increased deadspace ventilation. Furthermore, lateral positioning of patients is usually necessary for an optimal surgical approach and may contribute further to ventilation–perfusion mismatch resulting in compromised gas exchange. In order to prevent hypoxaemia and hypercapnia, repeated *in vitro* (laboratory) blood-gas analyses are performed frequently during OLV to control and adjust ventilation and oxygenation of the lungs. Continuous intra-arterial blood-gas monitoring would be advantageous because changes in oxygenation and carbon dioxide elimination can be recognized and treated immediately.[1]

The Paratrend 7 (Biomedical Sensors Ltd, Pfizer Hospital Products Group, High Wycombe, UK) is a fast-response intra-arterial blood-gas monitoring system which may be suitable for detection of rapid changes in arterial P_{O_2}, P_{CO_2} and pH values during thoracic surgery with OLV. It is currently the only commercially available intravascular blood-gas sensor system. The Paratrend 7 system (PT7), however, has been validated by only one group of authors in an experimental animal study[2] and, for limited P_{O_2}, P_{CO_2} and pH ranges, in the intensive care unit and during cardiac surgery.[3–5]

This study was performed to evaluate prospectively the clinical accuracy and performance of the Paratrend 7 intra-arterial blood-gas monitoring system during thoracoscopy over a wide range of PO_2, P_{CO_2} and pH values.

Patients and methods

Twenty-three patients undergoing elective thoracoscopic surgery gave their written informed consent to participate in this study, which was approved by the local Ethics Committee.

INTRAVASCULAR BLOOD-GAS SENSOR

The Paratrend 7 (PT7) is a multi-parameter sensor system incorporating four different sensors: P_{O_2} is measured by a miniaturized Clark electrode, P_{CO_2} and pH are measured by Optodes, and blood temperature is determined by a thermocouple. The four sensor elements are housed in a heparin-coated microporous polyethylene tubing of approximately 0.5 mm in diameter, suitable for insertion through a 20-gauge or larger size catheter. The tip with the sensor elements, approximately 4 cm in length, has to float freely in the arterial lumen. The device with the blood-gas sensor incorporates a tubing system enabling simultaneous continuous intravascular arterial pressure measurement and intermittent

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Andreas Zollinger, MD, Donat R. Spahn, MD, Thomas Singer, MD, Marco P. Zalunardo, MD, Simone Stoehr, MD, Thomas Pasch, MD (Institute of Anaesthesiology), Walter Weder, MD (Department of Surgery); University Hospital Zurich, CH-8091 Zurich, Switzerland. Accepted for publication: March 10, 1997.

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blood aspiration via a sideport for repeated *in vitro* laboratory blood-gas measurement. The disposable sensor is sealed by the manufacturer within a tonometer containing buffer solution, which maintains hydration and serves as a calibration medium. Before insertion into the patient, the sensor is calibrated under microprocessor control by the PT7 monitor using three precision gases bubbled through the tonometer. The calibration procedure takes 30 min. According to the manufacturer's guidelines, the sensor should be inserted into the artery within 8 h thereafter. Later, re-calibration of the system using the values of *in vitro* laboratory blood-gas determinations as a reference is only recommended every 12 h. After insertion of the calibrated sensor, the PT7 monitor provides continuous graphical and numerical display of the measured values $P\text{o}_2$, $P\text{co}_2$, and pH. Temperature and calculated values $S\text{o}_2$, HCO_3- and BE are displayed numerically.

Patients received oral premedication with midazolam 3.75–7.5 mg, 30–45 min before transfer to the operating theatre. After insertion of an 18-gauge i.v. cannula (Adsyte, Becton Dickinson Vascular Access Inc., UT, USA), a radial artery (left/right=16/7) was cannulated under local anaesthesia using a 5.1 cm long, 20-gauge catheter (Insyte, Becton Dickinson Vascular Access Inc., Sandy, UT, USA). A pressure transducer (Uniflow 43–600F, Baxter, Bentley Laboratories Europe, Uden, The Netherlands) was connected to the sideport of the previously calibrated PT7 sensor system for continuous intra-arterial pressure measurement. The pressure transducing tubes were prefilled with a solution of normal saline containing heparin 2 u. ml^{-1}. While flushing continuously from a pressurized flush bag, the sensor was inserted through the radial cannula, advanced to a depth of 15 cm and attached to the skin with adhesive tape. Any movements of the hand were prevented to avoid kinking of the PT7 sensor. The arterial pressure waveform was displayed on a Hellige monitor (VICOM-SM SMU 612, PPG Hellige, Freiburg, Germany) and the continuous intra-arterial blood-gas measurements displayed on the PT7 monitor. Additional routine monitoring of patients consisted of five-lead ECG, pulse oximetry, rectal temperature measurement and measurements of end-tidal concentrations of carbon dioxide and inhalation anaesthetics (all VICOM-SM SMU 612, PPG Hellige, Freiburg, Germany). Anaesthesia was induced using thiopentone and fentanyl i.v. Neuromuscular block was produced with suxamethonium. Left endobronchial intubation was performed with a double-lumen tube (Sher-I-Bronch, Sheridan Catheter Corp., Argyle, NY, USA) under fibreoptic control. Enflurane in oxygen and air, fentanyl and pancuronium were used for maintenance of anaesthesia and neuromuscular block. Volume-controlled ventilation was used (Siemens Servo 900 D ventilator, Siemens Life Support Systems, Solna, Sweden), and ventilatory patterns were adjusted by an experienced anaesthetist tailored to the individual patient. Positioning of patients was performed according to surgical needs (left lateral 14 patients; right lateral eight patients; supine one patient). To provide a collapsed lung on the side of operation, OLV with an inspired oxygen fraction of 1.0 was induced on the contralateral side before skin incision for introduction of the trocar through the seventh or eighth intercostal space, and maintained throughout thoracoscopy. At the end of surgery a drainage tube was inserted and the collapsed lung was again ventilated.

DATA COLLECTION

The PT7 sensor was inserted immediately after the initial calibration procedure was completed in all cases, and was not re-calibrated thereafter. Data were obtained after induction of anaesthesia, 5, 10, and 20 min after the onset of OLV, before the end of OLV, and 10 min after two-lung ventilation was re-established. Provided that system stability was indicated by the PT7 computer according to the manufacturer's manual, arterial blood-gas values displayed on the PT7 monitor were stored at these times. Simultaneously, a 1-ml blood sample was obtained for *in vitro* blood-gas analysis from the radial artery cannula using a pre-heparinized syringe (QS 50, Radiometer Medicals, Copenhagen, Denmark). *In vitro* measurement was performed within the next 2 min (IL 1400 BGE-analyzer with IL 482 co-oximeter, Instrumentation Laboratory, Milano, Italy) by a laboratory technician who was unaware of the *in vivo* PT7 values. Both PT7 and blood-gas analysis values were determined at 37 °C and thus no temperature correction was performed. Rectal and PT7 temperature readings were also recorded.

DATA ANALYSIS

All results were analysed using StatView 4.1 software (Abacus Concepts, Inc., Berkeley, CA) on an Apple Macintosh computer. Data are presented as mean (SD). Bias (mean of the differences PT7 − blood-gas analysis (BGA)) and precision (1.96 SD of these differences) were calculated[6] for arterial pH, $P\text{o}_2$, $P\text{co}_2$, $S\text{o}_2$, HCO_3-, BE and temperature. Simple linear regression analyses were performed for arterial $P\text{o}_2$, $P\text{co}_2$, SO_2, HCO_3-, BE and temperature, but not for pH because of its logarithmic scale. The pH values, instead, were converted to $[H^+]$, and linear regression analysis and calculation of bias and precision were performed. Furthermore, sequential changes in arterial PO_2, $P\text{co}_2$, pH and $[H^+]$ between two consecutive times (delta $P\text{o}_2$ delta $P\text{co}_2$, delta pH, delta $[H^+]$) were calculated for PT7 and BGA. Bias and precision of these changes were calculated for delta $P\text{o}_2$ delta $P\text{co}_2$, delta pH and delta $[H^+]$, and linear regression analyses were performed for delta $P\text{o}_2$, delta $P\text{co}_2$ and delta $[H^+]$. One-sample Sign tests were used to compare biases with the hypothesized ideal value of 0. $P<0.05$ was considered statistically significant.

Results

All 23 patients were studied (mean age 55 (range 20–76) yr; male/female ratio 17/6; ASA grade I, two patients, grade II, 12 patients, grade III, eight

Table 1 Arterial blood-gas values obtained by the Paratrend 7 monitor (PT7) and by simultaneous *in vitro* blood-gas analysis (BGA). Arterial $P\mathrm{O}_2$, $P\mathrm{CO}_2$ and pH were measured by both systems, HCO_3- and BE were calculated by both systems. $S\mathrm{O}_2$ was measured by the co-oximeter and calculated by the Paratrend 7. $n=138$

	Mean (SD)		Minimum		Maximum	
	PT7	BGA	PT7	BGA	PT7	BGA
$P\mathrm{O}_2$ (kPa)	24.3 (15.8)	24.0 (14.5)	5.7	6.1	72.9	61.1
$P\mathrm{CO}_2$ (kPa)	6.0 (0.8)	5.7 (0.9)	4.5	4.1	9.9	9.5
pH	7.37 (0.06)	7.39 (0.05)	7.19	7.19	7.47	7.50
HCO_3- (mmol litre^{-1})	25.9 (2.1)	25.6 (1.4)	21.4	21.3	33.5	28.8
BE (mmol litre^{-1})	0.6 (2.7)	1.0 (1.5)	−6.2	−4.5	8.6	3.7
$S\mathrm{O}_2$ (%)	97.0 (4.1)	95.3 (4.9)	78.7	73.8	99.9	99.7

Table 2 Results of comparisons between Paratrend 7 readings and simultaneous *in vitro* blood-gas determinations. Arterial $P\mathrm{O}_2$, $P\mathrm{CO}_2$ and pH were measured by both systems, HCO_3- and BE were calculated by both systems $S\mathrm{O}_2$ was measured by the co-oximeter and calculated by the Paratrend 7. $[\mathrm{H}^+]$ was calculated from the pH values measured by both systems to allow linear regression analysis. $n=138$. $^*P<0.05$, $^{***}P<0.0001$, compared with hypothesized ideal value of 0. Regression line equation $y=a+b\times x$: y=Paratrend 7 readings, x=*in vitro* blood-gas determinations, a=axis intercept, b=regression coefficient (slope), r=correlation coefficient

	a	*b*	*r*	Bias	Precision
$P\mathrm{O}_2$ (kPa)	−0.64	1.04	0.95	0.38	9.52
$P\mathrm{CO}_2$ (kPa)	1.04	0.87	0.90	0.31***	0.76
pH	—	—	—	−0.017***	0.065
HCO_3- (mmol litre $^{-1}$)	9.73	0.63	0.43	0.3*	3.9
BE (mmol litre $^{-1}$)	−0.36	1.00	0.56	−0.4	4.4
$S\mathrm{O}_2$ (%)	25.4	0.7	0.82	1.7***	5.5
$[\mathrm{H}^+]$ (nmol litre $^{-1}$)	4.69	0.93	0.84	1.76***	6.62

Table 3 Temperature obtained by the Paratrend 7 sensor in the radial artery (Temp PT7, °C) and by simultaneous rectal temperature measurement (Temp rect, °C). $n=138$. $^{***}P<0.0001$ compared with hypothesized ideal value of 0. Min/Max=Minimum/maximum values. Regression line equation $y=a+b\times x$: y=Paratrend 7 radial temperature measurement, x=rectal temperature measurement, a=axis intercept, b=regression coefficient (slope), r=correlation coefficient

	Mean (SD)	Min/Max	*a*	*b*	*r*	Bias	Precision
Temp PT7	35.6 (0.9)	32.0/37.2	9.55	0.72	0.48	−0.5***	1.6
Temp rect	36.1 (0.6)	34.5/37.5					

Table 4 Sequential changes in arterial blood-gas tensions between two consecutive times (delta $P\mathrm{O}_2$, delta $P\mathrm{CO}_2$, delta pH): results of comparisons between Paratrend 7 readings and simultaneous *in vitro* blood-gas determinations Delta $[\mathrm{H}^+]$ was calculated from the pH values measured by both systems to allow linear regression analysis. $n=115$.
No significant differences from the hypothesized ideal value of 0. Regression line equation $y=a+b\times x$: y=Paratrend 7 readings, x=*in vitro* blood-gas determinations, a=axis intercept, b=regression coefficient (slope), r=correlation coefficient

	a	*b*	*r*	Bias	Precision
Delta $P\mathrm{O}_2$ (kPa)	0.27	1.03	0.97	0.28	9.04
Delta $P\mathrm{CO}_2$ (kPa)	−0.01	0.87	0.87	0.01	0.59
Delta pH	—	—	—	−0.001	0.035
Delta $[\mathrm{H}^+]$ (nmol litre^{-1})	0.06	0.93	0.87	0.08	3.52

patients, grade IV, one patient). The operations performed were: lung resection (14), pleurectomy (six), bullectomy (two) and sympathectomy (one). Duration of anaesthesia was 220 (68) min, duration of operation was 106 (61) min and duration of OLV was 99 (58) min. All PT7 sensors calibrated and inserted into a radial artery measured intra-arterial blood-gas tensions throughout the study and there were no technical failures. According to the study design, six measurements in 23 patients were performed, producing 138 PT7 readings with corresponding blood-gas analysis values. Positioning of patients and diathermy did not affect sensor function. No complications attributable to the sensor were observed.

On average, near normal arterial $P\mathrm{CO}_2$ and high $P\mathrm{O}_2$ values were found (table 1). However, extreme blood-gas values were observed during thoracoscopic surgery and OLV, which offered the opportunity to study the accuracy of the PT7 over a wide range of blood-gas analysis values (table 1). PT7-$P\mathrm{O}_2$ corresponded very well with BGA-$P\mathrm{O}_2$, as evidenced by non-significant bias (0.38 kPa) and a correlation coefficient of 0.95 (table 2, fig. 1). Also, PT7-$P\mathrm{CO}_2$ corresponded well with BGA-$P\mathrm{CO}_2$, as documented by a bias of 0.31 kPa ($P<0.0001$) and a correlation

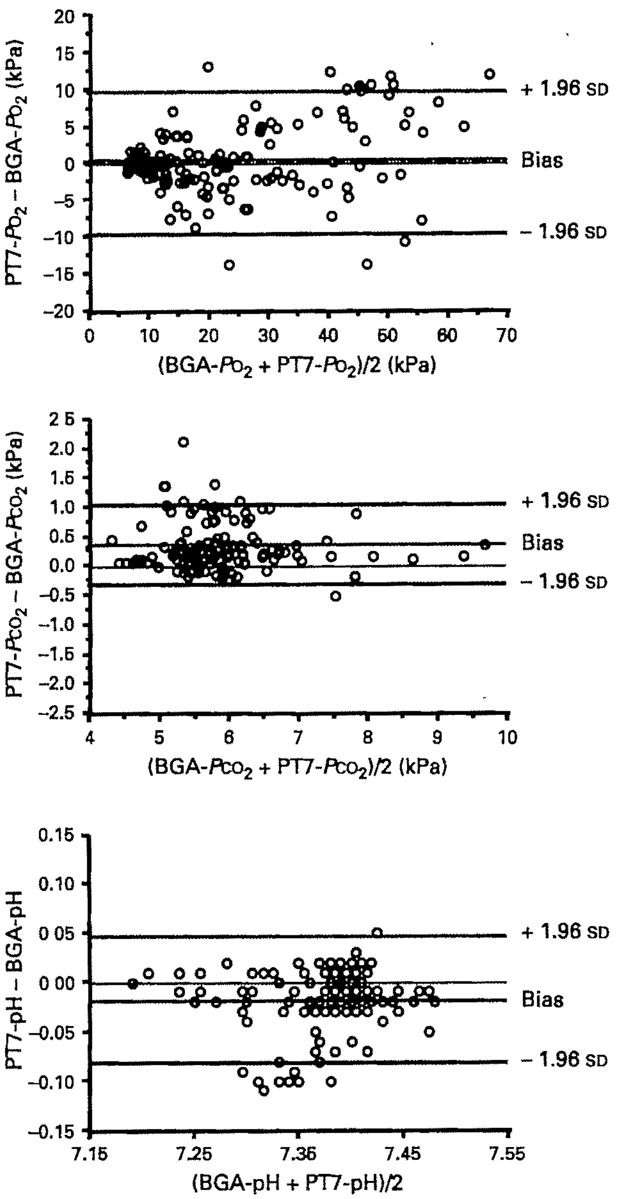

Figure 1 Bland Altman plots[6] showing bias (mean of differences) and precision (1.96 SD of these differences) *vs* mean values of arterial $P\mathrm{o}_2$, $P\mathrm{co}_2$ and pH obtained by Paratrend 7 (PT7) compared with values obtained by *in vitro* blood-gas measurement using a co-oximeter (BGA). $n=138$.

coefficient of 0.90 (table 2, fig. 1). Furthermore, the calculated $[\mathrm{H}^+]$ concentrations derived from the PT7-pH values correlated well with those derived from BGA-pH (correlation coefficient 0.84) (table 2). Bias between PT7-pH and BGA-pH was relatively small (-0.017; $P<0.0001$) (table 2, fig. 1). However, agreement of the calculated values $\mathrm{HCO_3^-}$ (0.43) and BE (0.56) was relatively poor (table 2). Mean PT7 radial temperature values were lower than those recorded rectally (table 3). The bias of the sequential changes between two consecutive times (delta $P\mathrm{o}_2$, delta $P\mathrm{co}_2$, delta pH, delta $[\mathrm{H}^+]$) was not significantly different from the hypothesized ideal value of 0 (table 4), and a good correlation coefficient between BGA and PT7 was found for the values delta $P\mathrm{o}_2$ (0.97), delta $P\mathrm{co}_2$ (0.87) and delta $[\mathrm{H}^+]$ (0.87) (table 4, fig. 2).

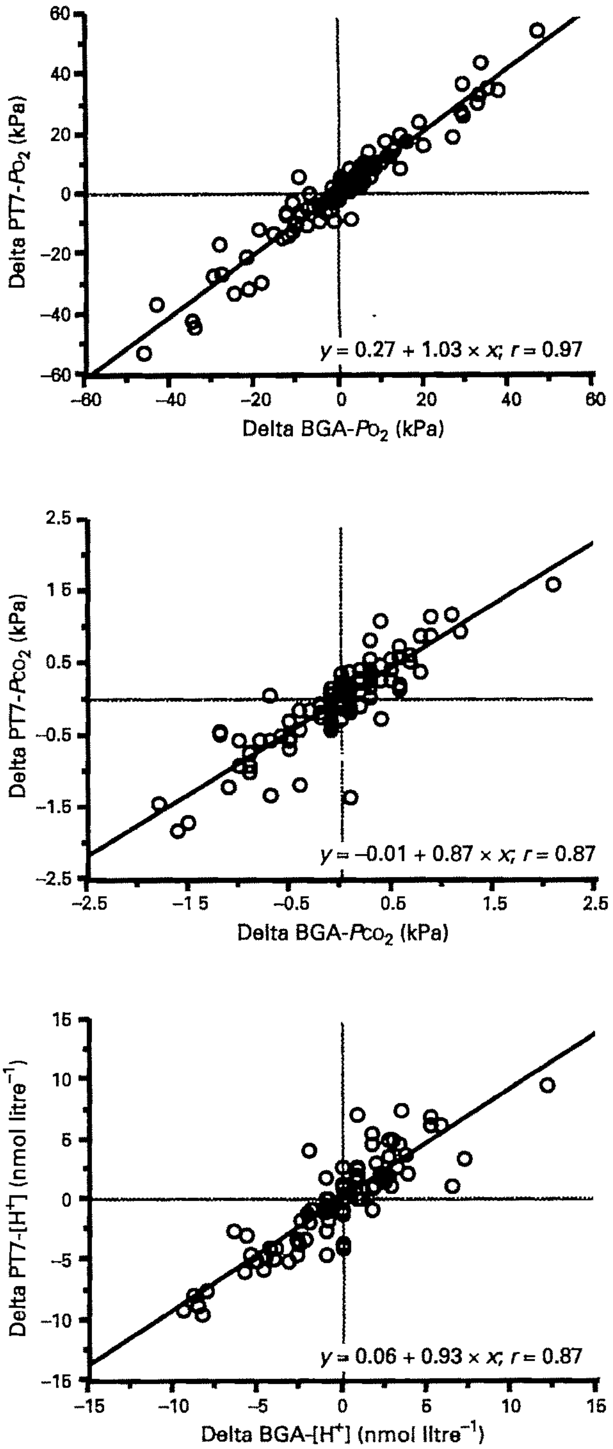

Figure 2 Linear regression analysis plots showing sequential changes in arterial $P\mathrm{o}_2$, $P\mathrm{co}_2$ and $[\mathrm{H}^+]$ between two consecutive times (delta $P\mathrm{o}_2$, delta $P\mathrm{co}_2$, delta $[\mathrm{H}^+]$) obtained by Paratrend 7 (PT7) *vs* corresponding changes obtained by *in vitro* blood-gas measurement using a co-oximeter (BGA). $n=115$.

Discussion

The results of this study indicate good clinical performance of the Paratrend 7 multi-parameter sensor. In all patients the sensor was inserted into the radial artery catheter without difficulties and accurately measured arterial blood-gas tensions continuously during thoracoscopy over a wide range of $P\mathrm{o}_2$, $P\mathrm{co}_2$ and pH values (see tables 1 and 2; fig. 1).

The correlation of So_2 values calculated by the PT7 compared with *in vitro* values determined by the co-oximeter was also satisfactory (table 2). However, radial PT7 temperature compared with rectal temperature (table 3), and values of HCO_3- and BE calculated by and displayed on the Paratrend 7 monitor showed poor correlation with those calculated from the *in vitro* blood-gas determinations (table 2).

Thoracoscopy necessitates OLV with close monitoring of arterial blood-gas tensions. Intermittent blood-gas measurement is currently standard care and insertion of an intra-arterial catheter is usually required. Although this represents a "continuously invasive" method, blood-gas determination is still only intermittent. Recently, serious shortcomings of conventional intermittent blood-gas analyses have been discussed.[7–10] The most obvious disadvantage is the dependence on clinical judgement as to when blood samples should be obtained. Adequate and immediate detection of serious events by the anaesthetist is presumed, blood has to be sampled in time and the results should be available rapidly. In many critical situations, however, blood sampling, transport and laboratory analysis is only possible with a considerable delay, and sampling rate is inherently limited. Thus intermittent blood-gas measurement represents a "snapshot" of a continuous physiological variable and is frequently obtained after a critical event has already occurred.[7] Continuous intra-arterial blood-gas monitoring, on the other hand, provides relevant physiological information on-line, including display of trends of measured variables. Furthermore, alarm limits for the variables may be defined. Continuous intra-arterial blood-gas monitoring is therefore desirable, provided that such a system is accurate.

Several clinical studies on the performance of intravascular sensor systems have been published[3–5 9–16] and the results have been reviewed recently.[17 18] None of these systems, however, is available commercially, except for the PT7. Unfortunately, the PT7 system has been validated clinically by only one team of investigators in collaboration with the manufacturer.[3–5] Assessing accuracy and clinical performance of the PT7 system independently is therefore important. In thoracoscopy, using OLV, we had the opportunity to assess the accuracy of the PT7 system over a wide range of arterial Po_2 (6.1–61.1 kPa), Pco_2 (4.1–9.5 kPa) and pH (7.19–7.50) values. We found good agreement of PT7 values and *in vitro* blood-gas analysis values for arterial Po_2, Pco_2 and pH (fig. 1, table 2). This is in keeping with previous studies in intensive care medicine[3] and cardiac surgery.[4 5] Furthermore, comparison of sequential changes between two consecutive times (delta Po_2, delta Pco_2, delta pH) showed good agreement (table 4, fig. 2), and no clinically relevant changes in PT7 values compared with changes in blood-gas analysis values were observed. This is of the utmost importance for a continuous monitoring system, as it is designed primarily to accurately reflect trends in measured variables.

Radial PT7 temperature was significantly lower than rectal temperature (table 3). This is not surprising as the radial artery may be considered an intermediate or even a peripheral temperature measuring site: core temperature is reflected more accurately by rectal rather than axillary temperature measurements during anaesthesia.[19] Therefore, both PT7 and blood-gas analysis values were determined at 37 °C in this methodological study. The PT7 system, however, offers the choice between measurement of blood-gas tensions at 37 °C (as performed in this investigation) and at patient (intravascular) temperature. Comparison of the two methods was not the object of this study.

Comparing PT7 and laboratory blood-gas analysis results is difficult because laboratory blood-gas analysis measurement is fraught with a variety of problems: samples for blood-gas analysis may easily be handled incorrectly by sample dilution, excess heparinized saline,[20 21] delays in analysis with the sample being stored at room temperature,[20 22] oxygen consumption from metabolism by leucocytes and other cells contained in the sample,[23] diffusion of gases through the plastic wall of syringes[24–26] and pressure of air bubbles in the samples,[22 26 27] particularly during transport.[28] In addition, the accuracy and variability of laboratory blood-gas analysers are not known exactly. The following criteria were applied in a recent evaluation of blood-gas analysers[29]: in the Po_2 range of 4–20 kPa and Pco_2 range of 2.7–10.6 kPa, respectively, 95% of measurements should be within $\pm 7.5\%$ or ± 0.6 kPa of a reference; for $Po_2 > 20$ kPa and $Pco_2 > 10.6$ kPa, respectively, 95% of measurements should be within $\pm 12.5\%$ of a reference; pH accuracy cannot be tested because there is no reference method.[29] Differences between PT7 and laboratory blood-gas values thus cannot *a priori* be considered to represent variability in the new method, that is the PT7, but may also result from errors in laboratory blood-gas analysis or in both of these methods.

The observed variability of PT7 Po_2, Pco_2 and pH measurements is acceptable for clinical decision making, and PT7 is a reliable trend indicator of arterial blood-gas tensions. During thoracoscopy with OLV, in selected cases, continuous intra-arterial blood-gas monitoring is therefore helpful in monitoring oxygenation and carbon dioxide. However, cost effectiveness and influence on outcome of this particular technology must be examined.[30 31] Whether the good clinical performance will translate into improved long-term outcome has not yet been investigated and requires further study.[32–34]

In summary, we found good accuracy and good clinical performance of the Paratrend 7 sensor system when used in patients during thoracoscopy. It appears to be a helpful tool in monitoring patients during surgical procedures associated with large variations in arterial blood-gas tensions, such as thoracoscopy with OLV.

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Midlatency auditory evoked potentials and motor signs of wakefulness during anaesthesia with midazolam

D. SCHWENDER, M. DAUNDERER, N. SCHNATMANN, S. KLASING, U. FINSTERER AND K. PETER

Summary

We have studied midlatency auditory evoked potentials (MLAEP) and motor signs of wakefulness during anaesthesia with midazolam in 10 patients undergoing elective laparotomy under continuous extradural analgesia. Anaesthesia was induced with midazolam 0.3 mg kg^{-1} and maintained with midazolam 0.3–0.9 mg kg^{-1} h^{-1}. Motor signs of wakefulness were documented as spontaneous movements and movements after simple commands (open eyes or move arms). MLAEP were recorded continuously awake, and during anaesthesia until the end of anaesthesia. Latencies of the peaks V, Na, Pa, Nb and P1 (ms) and amplitudes of the peaks Na/Pa, Pa/Nb and Nb/P1 (μV) were measured. Twenty-five movements were observed during anaesthesia; 15 movements in six patients were in response to commands. In two patients supplementary isoflurane was given. Latencies of the MLAEP peaks Pa, Nb and P1 increased slightly during anaesthesia. Amplitudes for Na/Pa, Pa/Nb and Nb/P1 did not change significantly. The high incidence of motor signs of wakefulness associated with preserved MLAEP indicated a high level of cortical neural activity and none of the MLAEP variables predicted movement during anaesthesia with midazolam. (*Br. J. Anaesth.* 1997; **79**: 53–58).

Key words
Hypnotics benzodiazepine, midazolam. Anaesthetics volatile, isoflurane. Monitoring, evoked potentials. Brain, evoked potentials.

The early auditory evoked potentials (AEP), generated in the brainstem, change only slightly during anaesthesia with volatile agents.[1–3] The late cortical components show great variation in latency and amplitude in the awake state and are not present during anaesthesia.[4 5] In contrast, midlatency peaks of the AEP do not differ appreciably either between individuals or over time. However, a range of anaesthetic agents depress midlatency auditory evoked potentials (MLAEP) in a dose-dependent manner.[1 2] Therefore, it has been suggested that MLAEP may be used to measure depth of anaesthesia and to indicate intraoperative awareness.[6 7] During induction of general anaesthesia with benzodiazepines, MLAEP appeared to be preserved compared with the awake state.[8] This observation may be relevant to occasional reports on intraoperative awareness during anaesthesia with benzodiazepines. In this study, we recorded MLAEP and motor signs of wakefulness continuously online while patients were awake and during anaesthesia with midazolam.

Patients and methods

After obtaining Institutional Ethics Committee approval and informed consent, we studied 10 patients, aged 20–60 yr, ASA I and II, undergoing elective laparotomy. After oral premedication with a benzodiazepine (clorazepate 20 mg), 45–60 min before anaesthesia, electrocardiograph electrodes (ECG) and an i.v. catheter were placed, and continuous extradural block was performed at L3–4 or L4–5. Using 0.5% bupivacaine the level of anaesthesia was maintained at T4–5. General anaesthesia was induced with midazolam 0.3 mg kg^{-1} i.v. After induction of anaesthesia and loss of consciousness (no response to verbal commands, loss of eyelid reflex) patient's lungs were ventilated with 100% oxygen via a face mask. Suxamethonium 1.0–1.5 mg kg^{-1} was given for neuromuscular block, the trachea intubated and controlled ventilation with 50% nitrous oxide in oxygen was commenced. No other neuromuscular blocking agents were used. To maintain general anaesthesia, patients received midazolam 0.3 mg kg^{-1} h^{-1} i.v. Heart rate (via a three-lead ECG), systemic arterial pressure (via an arterial cannula in the radial artery) and central venous pressure (via a catheter in the internal jugular vein) were recorded continuously. Mean arterial pressure was maintained at greater than 70 mm Hg. Body core temperature was measured by an oesophageal temperature probe and maintained at more than 35.5 °C using heated blankets and warmed infusions. Controlled ventilation was

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D SCHWENDER*, MD, M. DAUNDERER, MD, N. SCHNATMANN, MD, S. KLASING, U. FINSTERER, MD, K. PETER, MD, Institute for Anaesthesiology and University of Munich, Germany. Accepted for publication: March 7, 1997.

*Address for correspondence: Institute for Anaesthesiology, Ludwig-Maximilians-University, Munich, Klinikum Innenstadt, Nußbaumstraße 20, 80336 München, Germany.

adjusted to maintain normocapnia (end-expiratory $P\text{CO}_2$ 4.7–5.3 kPa) and verified by intermittent arterial blood-gas analysis. Doses of anaesthetics were guided by clinical signs of adequate anaesthesia (i.e. changes in arterial pressure, heart rate, sweating and tear production). Light anaesthesia was indicated by changes in the "pressure rate, sweating and tears" (PRST) score from baseline[9]. A PRST score greater than 2 or spontaneous movements of the patients were defined as indicative of light anaesthesia. Spontaneous movements of the head and arms, eye-opening or other facial movements were documented. Intermittently (every 10 min) patients were asked to follow simple commands (open eyes or move arms). If light anaesthesia was present, the infusion rate of midazolam was increased by 0.3 mg kg^{-1} h^{-1} up to 0.9 mg kg^{-1} h^{-1} i.v. When patients continued to show signs of light anaesthesia 10 min after the increase in midazolam infusion rate to 0.9 mg kg^{-1} h^{-1} i.v., anaesthesia was supplemented with 0.4–1.0 vol% isoflurane end-expiratory concentration. To evaluate conscious recall of anaesthesia and surgery, patients were asked at an informal postoperative interview to remember explicitly anything they may have perceived during anaesthesia.

The electrodiagnostic system Pathfinder I (Nicolet Instrument Corporation, Madison, WI, USA) was used for auditory stimulation, recording and analysis of evoked potentials. Rarefaction clicks of 0.1 ms duration and 70 dB greater than mean auditory threshold were presented binaurally with a stimulation frequency of 9.3 Hz using acoustically shielded earphones (TDH 39, Amplivox, Manchester, UK). For recording, silver electrodes were positioned at Cz and A_1/A_2 with Fpz as ground (according to the international 10–20 system). Impedance of all electrodes was maintained at less than 3 kΩ. Input signals were sampled at 5120 Hz during 100-ms post-stimulus epochs and averaged across 1000 stimulus presentations and digitally bandpass filtered (10–500 Hz). The recording procedure was controlled visually on a monitor, and an automatic artefact rejection procedure rejected signals greater than 96% of full scale. Line frequency suppression was set at 50 Hz. To guarantee correct transmission and transduction of the auditory stimuli, evoked potentials without a brainstem response (peak V) were rejected. Latencies of the peaks V, Na, Pa, Nb and P1 (ms) and amplitudes of Na/Pa, Pa/Nb and Nb/P1 (μV) were measured. For each observation, AEP of individual patients and a grand average calculated from individual AEP of all patients were generated. AEP were recorded continuously on-line while awake and during induction and maintenance of general anaesthesia, until the end of anaesthesia when patients' tracheas were extubated and they had recovered from anaesthesia. One AEP generated from 1000 responses with a stimulation rate of 9.3 represented approximately a 2-min period.

Results are presented as mean (SD). Cardiorespiratory variables and spontaneous movements were correlated by a time series analysis. For the peak latencies V, Na, Pa, Nb and P1 and amplitudes Na/Pa, Pa/Nb and Nb/P1, the Wilcoxon test was used. Statistical significance was assumed if $P<0.05$ after Bonferroni's correction for multiple comparisons.

Results

Patient characteristics, type and dose of premedication, type of surgery, total duration of surgery and anaesthesia, and total dose of bupivacaine given are presented in table 1. There were no significant changes in systolic and diastolic arterial pressures (SAP, DAP) or heart rate (HR) while awake, after induction or during maintenance of anaesthesia, or

Table 1 Patient characteristics and operative details (mean (SD) or number)

No. of patients	10
Age (yr)	48.88
Sex (F/M)	8/2
Weight (kg)	63.78 (15.87)
Height (cm)	163.22 (5.87)
ASA status	1.45 (0.50)
Type of surgery	
Abdominal hysterectomy	5
Exploratory laparotomy	5
Premedication	
Clorazepate bipotassium (mg kg/body weight)	0.29 (0.06)
Total dose of bupivacaine (mg kg/body weight)	2.32 (0.52)
Total duration of surgery (min)	194.3 (88.86)
Total duration of anaesthesia (min)	258.29 (100.09)

Table 2 Haemodynamic data while awake, during maintenance of anaesthesia and during emergence from anaesthesia (mean (SD)). HR=heart rate, SAP=systolic arterial pressure, DAP=diastolic arterial pressure. $*P<0.05$ compared with awake

	HR (beat min^{-1})	SAP (mm Hg)	DAP (mm Hg)
Awake	74 (13)	124 (20)	78 (10)
Maintenance of anaesthesia			
Anaesthesia (no movements)	72 (14)	110 (11)	66 (8)
8 min before movement	65 (11)	115 (22)	66 (8)
6 min before movement	67 (12)	117 (21)	67 (9)
4 min before movement	67 (11)	117 (19)	68 (9)
2 min before movement	70 (15)	118 (20)	68 (12)
Movement	73 (12)	122 (24)	73 (14)
Emergence from anaesthesia			
8 min before movement	60 (7)	115 (7)	63 (10)
6 min before movement	62 (7)	116 (11)	67 (10)
4 min before movement	63 (10)	118 (12)	65 (15)
2 min before movement	63 (7)	116 (13)	63 (14)
Movement	65 (8)	124 (25)	68 (17)

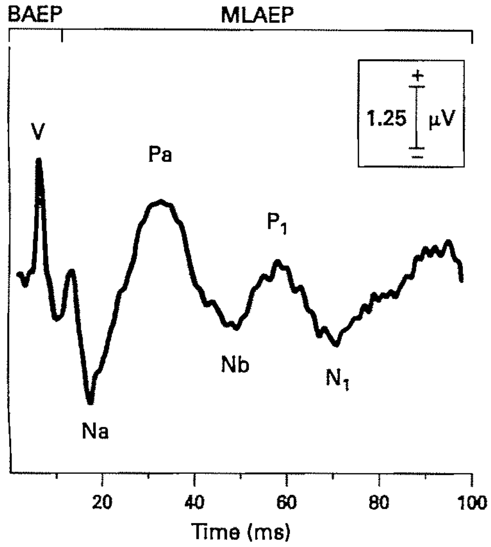

Figure 1 Auditory evoked potential of an awake patient. BAEP=Brainstem auditory evoked potential, MLAEP=midlatency auditory evoked potential.

during emergence from general anaesthesia (see table 2). We observed 25 movements (11 movements of the arm, 14 eye openings) during anaesthesia; 15 movements in six patients were in response to commands. One patient moved twice, two patients moved three times and two patients moved four times during anaesthesia. One patient had explicit recall of intraoperative events at the postoperative interview. In six patients the infusion rate of midazolam was increased and in two patients supplementary isoflurane was given. The trachea of all patients was extubated and patients regained consciousness at the end of anaesthesia. There were no correlations between haemodynamic data and movements observed during operation.

Figure 1 shows an original tracing of an AEP of an awake patient. Wave V is part of the brainstem generated potentials (BAEP); the MLAEP peaks Na, Pa, Nb, P1 show high amplitudes and a characteristic periodic waveform.

Figures 2 and 3 show typical original recordings of AEP of two individual patients while awake, during maintenance of anaesthesia (no movement) (figs 2A, 3A), during anaesthesia 8, 6, 4 and 2 min before and during intraoperative movement (figs 2B, 3B) and during emergence from anaesthesia (figs 2C, 3C). MLAEP of the awake patients had large amplitudes and a periodic waveform. During anaesthesia (no movements detected) latencies of the MLAEP peaks Nb and P1 increased only slightly with amplitudes of Na/Pa, Pa/Nb and Nb/P1 of MLAEP preserved (figs 2A, 3A). Before and during intraoperative movement, MLAEP did not change significantly compared with the preceding recordings during anaesthesia when no movements were seen. Nb and P1 were increased slightly compared with the awake state, and amplitudes Na/Pa, Pa/Nb and NB/P1 did not change significantly and were the same as those recorded in the awake state (figs 2B, 3B). The same pattern of MLAEP behaviour was observed during emergence from general anaesthesia (figs 2C, 3C).

Figure 4 shows the grand averages of the individual auditory evoked potentials awake, during anaesthesia with no movement observed (fig. 4A), during anaesthesia 8, 6, 4 and 2 min before and during intraoperative movements (fig. 4B), and during emergence from general anaesthesia (fig. 4C). MLAEP of the awake patients showed large peak-to-peak amplitudes and a periodic waveform. During anaesthesia with no movements observed, there was a slight increase in MLAEP latencies. MLAEP amplitudes were preserved (fig. 4A) before and during intraoperative movements. MLAEP did not

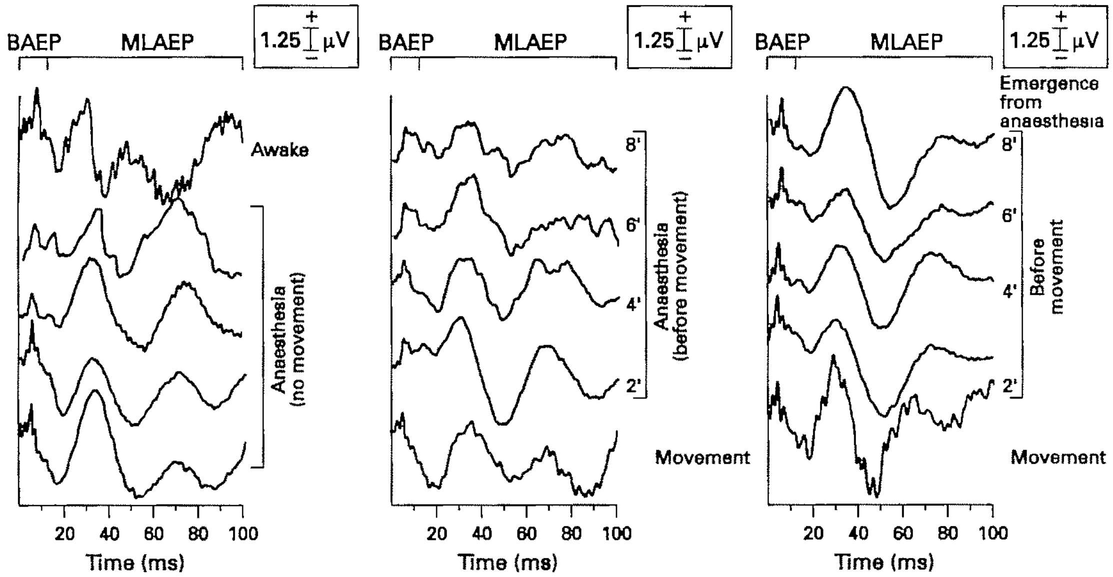

Figure 2 Auditory evoked potentials of an individual patient while awake, during anaesthesia with no movement observed (A), during anaesthesia 8, 6, 4 and 2 min before and during intraoperative movements (B), and during emergence from general anaesthesia (C). BAEP=Brainstem auditory evoked potential, MLAEP=midlatency auditory evoked potential. MLAEP of the awake patient had large amplitudes and a periodic waveform. During maintenance of anaesthesia MLAEP increased only slightly in latencies with amplitudes preserved. Before and during patient movements, observed during operation or during emergence from anaesthesia, amplitudes of the MLAEP were the same as those recorded while awake.

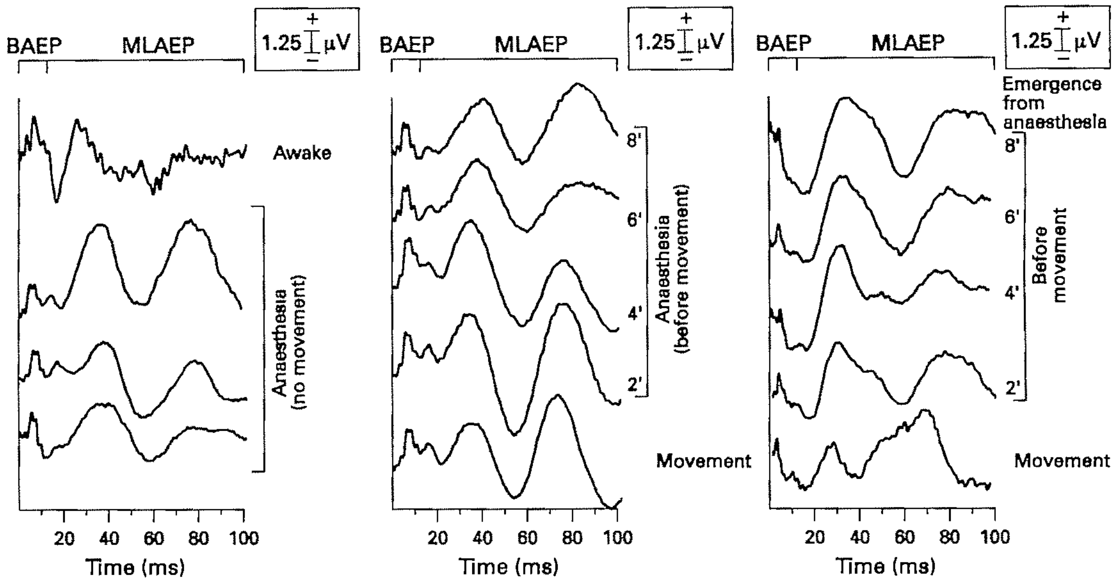

Figure 3 Auditory evoked potentials of a second individual patient while awake, during anaesthesia with no movement observed (A), during anaesthesia 8, 6, 4 and 2 min before and during intraoperative movements (B), and during emergence from general anaesthesia (C). Abbreviations and features as in figure 2.

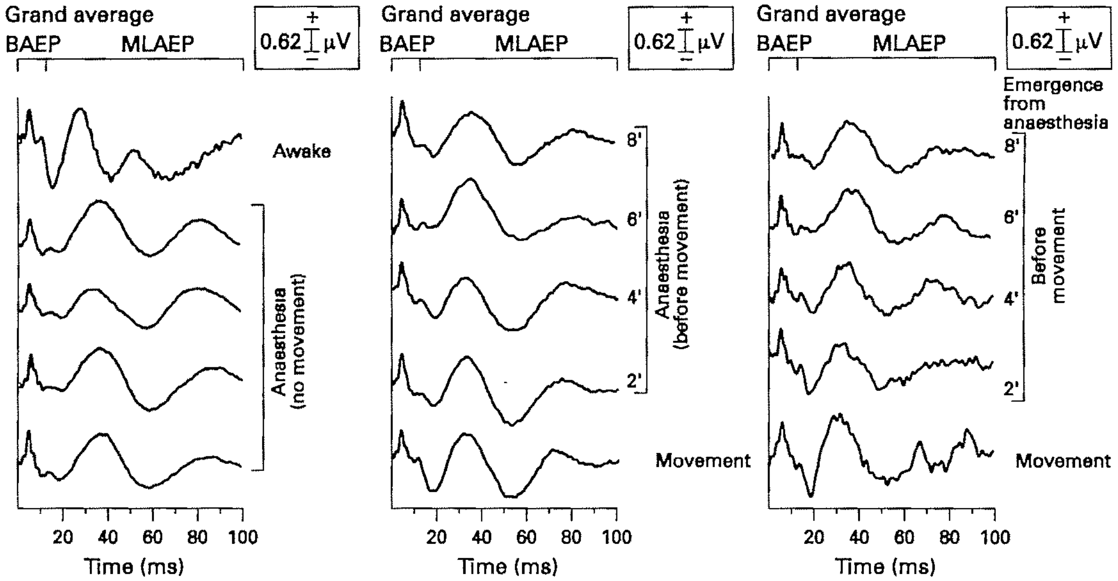

Figure 4 Grand averages of individual auditory evoked potentials while awake, during anaesthesia with no movement observed (A), during anaesthesia 8, 6, 4 and 2 min before and during intraoperative movements (B), and during emergence from general anaesthesia (C). BAEP=Brainstem auditory evoked potential, MLAEP=midlatency auditory evoked potential. Anaesthesia did not lead to significant suppression of MLAEP. When movements were observed, MLAEP showed a similar pattern as in the awake state before operation.

change compared with the preceding recordings during anaesthesia and were the same as in the awake state (fig. 4B). The same pattern was observed during emergence from anaesthesia (fig. 4C).

Mean values of the latencies of V, Na, Pa, Nb and P1 and amplitudes of Na/Pa, Pa/Nb and Nb/P1 while awake, during anaesthesia with no movement observed, 8, 6, 4 and 2 min before and during intraoperative movements, and during emergence from general anaesthesia are presented in table 3. There was a significant increase in the latencies of Pa (+20%), Nb (+33%) and P1 (+43%) during anaesthesia, with no movement observed compared with the awake state. Before and during intraoperative movement and movement during emergence of anaesthesia, latencies of Pa, Nb and P1 did not change significantly compared with anaesthesia with no movement observed. Compared with the awake state, Pa increased significantly at 8 min and at 8, 6 and 2 min before movement, respectively; Nb and P1 latencies increased significantly 8, 6, 4 and 2 min before and during movement observed during operation, and during emergence from anaesthesia. Amplitudes of Na/Pa, Pa/Nb and Nb/P1 did not change significantly during anaesthesia with no movement observed, before and during movement observed during operation, and during emergence from anaesthesia.

Table 3 Mean (SD) latencies of V, Na, Pa, Nb and P1 (ms) and amplitudes of Na/ Pa, Pa/ Nb and Nb/P1 (µV) while awake, during maintenance of anaesthesia and during emergence from anaesthesia. *$P<0.05$ compared with awake

	V	Na	Pa	Nb	Pl
Awake	6.21 (0.4)	18.03 (4.1)	31.33 (5.8)	44.09 (7.3)	57.00 (9.2)
Maintenance of anaesthesia					
Anaesthesia (no movements)	6.51 (0.4)	21.17 (2.5)	37.50 (2.7)*	58.60 (6.6)*	81.58 (4.5)*
8 min before movement	6.52 (0.4)	20.93 (1.7)	37.01 (2.7)*	57.38 (3.3)*	78.83 (7.3)*
6 min before movement	6.51 (0.4)	20.68 (2.5)	36.22 (2.9)	57.72 (5.4)*	82 37 (8.8)*
4 min before movement	6.45 (0.4)	21.07 (2.6)	36.52 (2.8)	55.19 (4.1)	80.35 (8.0)*
2 min before movement	6.45 (0.4)	20.23 (1.7)	36.06 (3.4)	57.35 (6.6)*	81.74 (9.2)*
Movement	6.45 (0.4)	21.90 (3.5)	36.38 (2.9)	56.57 (4.8)*	77.73 (8.8)*
Emergence from anaesthesia					
8 min before movement	6.61 (0.7)	22.40 (3.2)	39.75 (4.3)*	58.00 (7.1)*	79 53 (3.3)*
6 min before movement	6.79 (0.4)	22.00 (2.8)	38.55 (3.6)*	56.14 (6.7)*	74.96 (5.2)*
4 min before movement	6.65 (0.7)	20.58 (1.3)	36.07 (2.5)	56.20 (7.6)*	74.93 (5.0)*
2 min before movement	6.94 (0.5)	20.53 (2.2)	37.71 (4.5)*	56.24 (7.5)*	78.12 (7.1)*
Movement	6.86 (0.5)	19.67 (2.3)	34.66 (3.3)	53.46 (6.9)	73 08 (7.9)*

	Na/Pa	Pa/Nb	Nb/P1
Awake	1.23 (0.4)	1.33 (0.6)	1.09 (0.6)
Maintenance of anaesthesia			
Anaesthesia (no movements)	0.96 (0.2)	1.19 (0.3)	0.97 (0.2)
8 min before movement	0.93 (0.5)	1.14 (0.5)	0.86 (0.5)
6 min before movement	0.95 (0.4)	1.16 (0.4)	0.75 (0.5)
4 min before movement	0.90 (0.3)	1.14 (0.4)	1.08 (0.4)
2 min before movement	1.13 (0.4)	1.39 (0.5)	1.03 (0.8)
Movement	1.13 (0.5)	1.29 (0.4)	1.15 (0.6)
Emergence from anaesthesia			
8 min before movement	1.09 (0.5)	1.26 (0.5)	1.00 (0 5)
6 min before movement	1.21 (0.8)	1.08 (0.2)	0.73 (0.3)
4 min before movement	1.48 (0.6)	1.43 (0.4)	1.21 (0.3)
2 min before movement	1.45 (0.7)	1.18 (0.5)	1.16 (0.3)
Movement	2.19 (1.5)	2.03 (0.3)	1.58 (0.4)

Discussion

There was no correlation in our study between physiological signs of wakefulness (increase in heart rate and arterial pressure) and motor signs of wakefulness during a combination of extradural analgesia with bupivacaine and general anaesthesia with midazolam. This observation may be explained by the extensive extradural block in all patients during surgery. It interfered with cardiovascular variables by attenuating arterial pressure responses. In this study we combined regional and general anaesthesia to provide analgesia and to minimize the effect of pain on the level of arousal.

There was a high incidence of movements during anaesthesia in our study. Twenty-five movements were observed in 10 patients; 15 movements in six patients were in response to commands indicating a high incidence of apparent consciousness during anaesthesia with midazolam. Nevertheless, to test consciousness we used simple questions ("open eyes", "move arms") that were not cognitively taxing. Simple commands followed by progressively more taxing commands, for example "squeeze your fingers twice", which require a more cognitively aware patient to achieve a positive response were not used. Therefore, these data did not discriminate between simple and complex responses. Only one patient had explicit recall of intraoperative events which may be explained by the amnesic effect of midazolam. Our observations agree well with data obtained by Russel.[10] Russell used an isolated forearm technique and found that 72% of patients receiving midazolam and alfentanil for general anaesthesia were conscious at some time during surgery. Russell could not demonstrate any relationship between autonomic signs by the PRST score and motor signs of wakefulness.

In our study, latencies of the peaks V, Na, Pa, Nb and P1 showed small SD values and corresponded well with peak latencies obtained under experimental conditions.[5 11] Relative amplitudes of the components Na/Pa, Pa/Nb and Nb/P1 were within the normal range also and showed greater inter-individual variability than latencies. During anaesthesia with midazolam, MLAEP were preserved compared with the awake state. MLAEP latencies increased only slightly while amplitudes did not decrease. Several investigators have demonstrated that the generators of MLAEP are located in the primary auditory cortex of the temporal lobe.[5 12–15] This leads to the conclusion that with midazolam, the neural generators in the primary cortex of the temporal lobes are not suppressed completely and cortical processing of auditory stimuli remains intact to some extent.

In contrast with midazolam, many anaesthetic agents suppress MLAEP. It is a well known observation that MLAEP typically show a dose-dependent increase in latencies and a decrease in amplitudes during anaesthesia with isoflurane, enflurane, halothane, sevoflurane, desflurane, etomidate, thiopentone, propofol and Althesin.[1–3 16–22] At approximately 1 MAC of the volatile anaesthetics, isoflurane, sevoflurane and desflurane MLAEP components were severely attenuated or suppressed almost completely. The latencies of the brainstem components of the auditory evoked potential were prolonged only slightly. Therefore, it has been suggested that MLAEP may be used to measure depth of anaesthesia and indicate intraoperative awareness.[6 7]

There are experimental data from several studies indicating a close relationship between MLAEP and intraoperative movements, intraoperative awareness and explicit and implicit memory functions during general anaesthesia. After bolus injections of thiopentone, MLAEP were suppressed immediately after induction of general anaesthesia. Amplitudes and latencies of the MLAEP returned to awake baseline values 4–6 min after administration of thiopentone when patients demonstrated motor signs of wakefulness.[18] In patients undergoing Caesarean section, MLAEP indicated periods of intraoperative wakefulness and correlated with postoperative recall of surgical manipulations.[23] Thornton and colleagues[6] and Newton and colleagues[7] studied the relation between MLAEP and response to verbal commands, conscious awareness and recall in surgical patients and anaesthetized volunteers during different sub-MAC concentrations of nitrous oxide and isoflurane. When MLAEP peak latencies were increased significantly compared with the awake state, no response to verbal commands, conscious awareness or recall were observed. In contrast, when MLAEP were increased only slightly during anaesthesia they found a high incidence of response to verbal commands, conscious awareness and recall. The AEP variables were related to the level of wakefulness and reflected episodes of wakefulness more closely than end-expiratory blood-gas concentrations. Furthermore, it was shown that during phases of intact MLAEP in patients undergoing cardiac surgery, presented acoustic information in the intraoperative period could be perceived and remembered implicitly in the postoperative interview although patients had marked amnesia for the intraoperative message.[24]

We conclude that a high incidence of motor signs of wakefulness and consciousness associated with preserved MLAEP indicate a high level of cortical neural activity and responsiveness during anaesthesia with midazolam. Our data agree with those of Russell who concluded that "this i.v. anaesthetic technique cannot be recommended for general use".[10]

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Intradermal compared with prick testing in the diagnosis of anaesthetic allergy

M. McD Fisher and C. J. Bowey

Summary

We have tested the hypothesis that intradermal testing is a more effective method for determining the drug responsible for anaesthetic anaphylactic reactions than prick testing in 212 consecutive patients, aged more than 10 yr, referred to an anaesthetic allergy clinic over a 4-yr period. The study was a prospective, non-randomized design. Intradermal testing was conducted using a previously described method and diluted drugs, and prick testing using undiluted drugs (with the exception of opioid analgesics which were diluted 1:10). The tests were performed on individual patients' forearms on the same occasion. Patients were followed-up to determine the results of subsequent anaesthesia and the difference between tests was analysed using kappa and tau statistics. There was 93% agreement overall between the paired tests. Which test detected the drug responsible was dependent on diagnostic criteria for positivity. The differences between the tests were not statistically significant. Using both tests improved predictability by 67% (tau=0.67, $P<0.001$). We conclude that in the absence of data to support one test being superior, other factors influence the choice of test. Prick testing was cheaper, and the reduction in pain and trauma with prick testing makes it more suitable for children. However, there are no data available on the safety of subsequent anaesthesia based on the results of prick testing alone, and reliability with time has not been assessed. Intradermal testing may be easier for the infrequent user. Skin testing is valuable in the investigation of anaesthetic anaphylaxis whichever test is chosen. When there is doubt both tests should be performed. (*Br. J. Anaesth.* 1997; **79**: 59–63).

Key words
Allergy. Skin, tests. Complications, anaphylaxis.

The use of skin testing to verify the anaphylactic aetiology of an adverse event during anaesthesia, establish the drug responsible and predict the safety of alternative drugs has been validated in several studies.[1–7] The high incidence of positive radioimmunoassay (RIA) tests for specific IgE to induction agents and neuromuscular blocking drugs in patients with positive skin tests[8 9] suggests that these tests demonstrate IgE antibodies to drugs which give positive tests and that the reactions in which the tests are positive are IgE-mediated.

Controversy persists as to the best method of skin testing. Intradermal testing has been used in the majority of studies, although three studies have demonstrated that prick testing has a similar efficacy.[10–12] In a prospective comparison of prick and intradermal testing in the same patients, Leynadier and colleagues[11] suggested that prick testing was the better test although seven of 50 reactors with positive intradermal tests had negative prick tests. Laxenaire and colleagues found no difference in the results in 34 patients using serial dilutions of drugs.[10]

To evaluate these tests further, we have investigated prospectively 212 patients referred to an anaesthetic allergy clinic for investigation of possible anaesthetic allergy.

Patients and methods

Over a 4-yr period, we investigated 212 consecutive adult patients referred to the anaesthetic allergy clinic. Children less than 10 yr of age and patients who allegedly reacted to local anaesthesia were excluded. The hospital Ethics Committees did not require informed consent for testing as it was considered that both tests were valid diagnostic tests.

For intradermal testing, drugs were freshly diluted in normal saline the day of the test and testing was performed using a design described previously.[2] Table 1 shows the dilutions used for the first 102 patients (group I) and the second 110 patients in whom dilutions of the neuromuscular blocking drugs were increased (group II) to determine if this affected the results of testing. All drugs used before the reactions were tested, and in the case of neuromuscular blocking agents the other available blockers were tested. This availability varied over the course of the study. Gallamine was used only if it had been administered before the reaction.

Malcolm McD Fisher, mb, chb, md, frca, fanzca, University of Sydney, Intensive Therapy Unit, Royal North Shore Hospital of Sydney, St Leonards, NSW, Australia 2065. C. Jane Bowey, rn, Intensive Therapy Unit, Royal North Shore Hospital of Sydney, St Leonards, NSW, Australia 2065. Accepted for publication: February 26, 1997.

Correspondence to M. F.

Table 1 Drug dilutions for skin testing and number of comparisons

Drug	Standard dilution	Group 1 Intradermal test	Group 2 Intradermal test	Group 3 Prick test	Times used
Morphine	10 mg ml^{-1}	1:100 000	1:100 000	1:10	9
Pethidine	50 mg ml^{-1}	1.100 000	1:100 000	1:10	6
Papaveretum	20 mg ml^{-1}	1:100 000	1:100 000	1:10	3
Fentanyl	100 μg/ml^{-1}	1:100	1:100	Undilute	36
Thiopentone	25 mg ml^{-1}	1:100	1:100	Undilute	175
Methohexitone	10 mg ml^{-1}	1:100	1:100	Undilute	2
Propofol	10 mg ml^{-1}	1:100	1:100	Undilute	20
Diazepam	5 mg ml^{-1}	1:100	1:100	Undilute	3
Midazolam	5 mg ml^{-1}	1:100	1:100	Undilute	1
Suxamethonium	50 mg ml^{-1}	1:1000	1:500	Undilute	167
Alcuronium	5 mg ml^{-1}	1:1000	1:500	Undilute	166
Atracurium	10 mg ml^{-1}	1:10000	1:1000	Undilute	145
Tubocurarine	10 mg ml^{-1}	1:10000	1:1000	Undilute	143
Gallamine	40 mg ml^{-1}	1:1000	1:500	Undilute	4
Vecuronium	4 mg ml^{-1}	1:1000	1:500	Undilute	146
Pancuronium	2 mg ml^{-1}	1:1000	1:500	Undilute	144
Neostigmine	2.5 mg ml^{-1}	1:1000	1·1000	Undilute	7
Atropine	0.6 mg ml^{-1}	1:1000	1:1000	Undilute	10
Cephalothin	100 mg ml^{-1}	1:100	1:100	Undilute	7
Cefotaxime	50 mg ml^{-1}	1:100	1:100	Undilute	1
Haemaccel	3.5 mg ml^{-1}	1:100	1:100	Undilute	5
Dextran 70	6 mg ml^{-1}	1:100	1:100	Undilute	2
Histamine	1:50	1:50	1:50	Undilute	170
Droperidol	10 mg/2 ml	1:100	1:100	Undilute	3
Penicillin	1 000 000 u/5 ml	1:100	1:100	Undilute	3
Protamine	500 mg/10 ml	1:1000	1:1000	Undilute	2
Gentamicin	80 mg/2 ml	1:100	1:100	Undilute	3

For prick testing, the drug solution was placed on the ventral aspect of the forearm and the epidermis pricked through the solution using a 25-gauge needle, bevel uppermost at 45 °C to the skin, to a depth at which the skin could be lifted. Morphine, papaveretum and pethidine were diluted 1:10 in saline as preliminary studies suggested that false positives were caused by these drugs if undiluted. All other drugs were undiluted (table 1).

For intradermal testing, a positive result was recorded for a persistent wheal of greater than 0.8 cm and for the prick testing a positive result was recorded for a wheal of greater that 0.4 cm. If the test was positive for a drug administered before the reaction being investigated the result was recorded as diagnostic, that is caused by that drug. The agreement between tests was assessed statistically using Kappa[13 14] and Tau[15] tests.

All patients were given a letter describing the event and the results of testing, and details of subsequent anaesthesia were sought.

The patients were divided in four groups: *minor reactions*—29 patients had reactions confined to the skin, or systemic reactions which resolved rapidly without treatment; *severe reactions*—135 patients had systemic reactions requiring treatment with vasoactive drugs; 129 of these were felt by the anaesthetist to have been life threatening; *preoperative*—13 patients were referred because of multiple allergies and were to undergo anaesthesia; *not anaphylactic*—35 patients had single system reactions in which another cause (assessed by an independent physician from the history) was likely.

Results

The results for all patients are shown in table 2. Overall there was agreement for 1294 (93%) comparisons and disagreement for 98 (7%); there was no significant difference between the agreement in the different groups.

The highest diagnostic yield was in patients with severe reactions in which a diagnosis was made in 116 of 135 patients. The majority of these patients reacted to neuromuscular blocking drugs (93 patients), and the other drugs implicated by skin testing were induction agents (13 patients), induction agent with neuromuscular blocking agent (two patients), antibiotics (three patients) opioid analgesics (three patients)and Haemaccel (two patients). Intradermal testing in this group was positive for more drugs than prick testing overall, but less when

Table 2 Prick testing and intradermal testing in 212 patients: overall results

Group	No.of patients tested	No. of comparisons	Drug responsible detected					Agreement between tests	
			Prick	Intradermal	Both	Either	Neither	Agree (%)	Disagree (%)
Minor reactions	29	117	8	5	4	9	20	113 (97%)	4 (3%)
Severe reactions	135	965	108	112	104	116	19	890 (92%)	75 8(%)
Preop.	13	82	1	1	0	2	11	75 (90%)	7 (9%)
Not anaphylactic	35	228	0	0	0	0	35	216 (95%)	12 (5%)
Total	212	1392	117	118	108	127	85	1294 (93%)	98 (7%)

Table 3 Prick *vs* intradermal testing for severe reactors. Changing diagnostic criteria to any response to prick test positive

	No.	Prick test positive	Intradermal positive	Both positive	Either positive	Neither positive	Agree	Disagree
Criterion I								
Wheal >4mm =+	135	108	112	104	116	19	890 (92%)	75 (8%)
Criterion II								
Any wheal =+	135	115	112	106	112	14	855 (89%)	110 (11%)

Table 4 Effects of altering intradermal test concentration on reliability of tests in patients with severe reactions

	No.	Prick test positive	Intradermal positive	Both positive	Either positive	Neither positive	Agree	Disagree
Test I								
Normal concn	74	58	63	57	64	10	518 (93.50)	36 (6.50)
Test II								
Increased concn	61	50	49	47	52	9	372 (90.50)	39 (9.50)

Table 5 Results of subsequent anaesthesia in patients tested by prick and intradermal testing.

Group	*n*	Subsequent GA uneventful	Subsequent
Minor reactions	29	10	0
Severe reactions			
Drug determined	116	65	1
Skin tests negative	19	17	0
Preoperative	13	12	0
Not anaphylaxis	35	20	0

prick test results were considered positive if wheal size was less than 4 mm (table 3). This increase with prick testing was not statistically significant. The agreement between intradermal and prick teasing was substantial in the severe group (kappa=0.7) and excellent overall (kappa=0.8).

In spite of this degree of agreement, the tau analysis suggested a 50% reduction in predictive error if both tests were used in the severe group (tau=0.5, $P<0.001$) and a reduction in predictive error of 67% if both tests were used in all patients (tau=0.67, $P<0.001$).

The majority of disagreement in reactions to neuromuscular blocking drugs was not in the drug responsible but in the detection of cross sensitivity to other neuromuscular blocking agents. In the severe group of patients, increasing the concentration of neuromuscular blocking agent did not alter significantly the diagnostic yield of the test (kappa=0.73 *vs* kappa=0.68) (table 4).

Details of subsequent anaesthesia were obtained in 124 patients (table 5). One patient had a second reaction. This patient, who reacted to pancuronium, had positive prick and intradermal tests to pancuronium and a subsequent reaction to which we attributed to alcuronium on the basis of history. Both tests were negative for alcuronium after both reactions. One patient had a minor systemic reaction after testing with thiopentone and histamine only, and this responded to adrenaline 0.2 mg s.c.

Discussion

The major problem with studies of this nature is that there is no absolute measure with which to compare the results.[16] Thus when there is disagreement it is not possible to tell which test is correct, without subjecting the patient to the hazards of challenge. As RIA tests are less sensitive and specific than skin tests,[16] they are not suitable to discriminate between tests which disagree, although when positive for an individual drug they add support to the skin test diagnosis.

We have shown previously that basing subsequent anaesthesia on diagnosis and detection of cross sensitivity from intradermal testing is usually reliable, with only three anaphylactic reactions in subsequent anaesthesia in 234 patients who had life-threatening reactions before testing.[16] The data from this study confirm that in patients with anaphylaxis during anaesthesia, subsequent anaesthesia based on the results of prick and intradermal testing is usually, but not always, safe. There have been no published studies showing the safety or otherwise of subsequent anaesthesia based on the results of prick tests alone.

Galletly[17] suggested that the dilutions chosen in our studies for intradermal testing (which were chosen by determining dilutions that did not cause wheals as a result of direct histamine release in volunteers) were greater than necessary. This could be a source of false negative results. Increasing the concentrations of neuromuscular blocking agents for intradermal testing did not significantly alter the diagnostic value of the test but increased the discrepancy between prick and intradermal tests for other neuromuscular blocking agents. The majority of this increase was related to reactions to the potent cutaneous histamine releasers tubocurarine and atracurium.

The diagnostic criteria for positivity were fulfilled more often by intradermal testing than by prick testing when a positive result for prick testing was a wheal greater than 4 mm. Moneret Vautrin and Laxenaire[18] have suggested that any wheal should be considered positive for prick testing and, using this criterion, prick testing produced a diagnostic result more commonly than intradermal testing. It cannot be determined however whether this was an increase in false positives or true allergy detected. Both tests produced more diagnoses than each test alone, and the statistical analysis suggested the safety of subsequent anaesthesia would be improved by performing both tests.

There is little to choose between each test on the basis of the above data in which a single intradermal test was used for each drug, rather than the serial dilutions used in the French study which showed 100% agreement in 38 patients.[10] It is possible that using serial dilutions rather than a single injection would increase the diagnostic value of intradermal testing even further.[10 18]

Prick testing has advantages over intradermal testing: it is cheaper than intradermal testing (by approximately 25% in our unit); the reduced pain and trauma of prick testing makes it more suitable for use in children; and it is said to be safer.[18] There are no data to support this view for anaesthetic drugs. Indeed the low incidence of systemic reactions to skin testing after anaesthetic reactions (three in more than 1200 patients in our series) would imply that a very large study is necessary to show a significant difference.

It has been suggested that intradermal tests are more likely to produce false positives than prick tests.[18] This would favour the use of intradermal tests, as a false positive test inconveniences the anaesthetist and does not carry the risk of anaphylaxis of a false negative test.[8] Intradermal testing is more reliable in propofol reactions.[19]

Intradermal testing has been validated in repeat studies over time[20 21] but no data are available for prick testing. The study of Leynadier, Sansarricq and Dry[21] suggested that the persistence of positive tests was insufficiently reliable on which to base subsequent drug selection and further preoperative skin tests should be performed, but our own study[20] and the anaesthetic follow-up of allergic patients,[16] suggest that the positive tests persist for up to 30 yr and preoperative testing is only mandatory if untested drugs to which the patient may show cross sensitivity are to be used.

One other practical factor worthy of consideration is ease of performance. We believe that the anaesthetist who is not regularly testing patients would find intradermal testing easier to perform and interpret.

It is important to emphasize that history is also very important in the follow-up of patients with possible anaesthetic allergy. In 19 patients with a severe reaction in whom a diagnosis was not made with skin testing, a diagnosis could be made from history or RIA testing in 17 of 19 cases. In six patients with a negative skin test, the diagnosis could be made from the history as only one drug was administered within 10 min of the reaction. Two patients had negative cutaneous responses to histamine controls and had a diagnosis made by RIA testing. One patient who had previous skin and RIA testing was re-tested 7 yr later and all tests were negative; we concluded that sensitivity had been lost. Two patients had strongly positive RIA and skin tests for neuromuscular blocking agents other than the one administered and one patient who had reacted to decamethonium and suxamethonium on separate occasions had strongly positive RIA to suxamethonium and positive skin tests to decamethonium only. She was not re-tested with decamethonium as it is no longer available. (She has subsequently had a positive intradermal test to suxamethonium 3 yr later.) In these three patients we suggested that all positive drugs and the one used should be avoided.

Three other patients had intradermal tests implicating a drug used, but not reaching the criterion for positivity in this study, and were warned against the drugs suggested. One patient had a negative mast cell tryptase test and negative skin tests, making an anaphylactic aetiology unlikely. One patient, who was tested only for thiopentone and histamine as thiopentone was the sole agent used, had negative skin tests but a mild anaphylactic reaction. In only two patients who had severe reactions could no aetiological agent be found. Both of these patients and 15 of the others who did not the meet criteria for positive skin tests have undergone subsequent uneventful anaesthesia.

In patients referred before operation, one patient had a positive prick test but not intradermal test to three drugs and one patient had a positive intradermal test but not a prick test to three neuromuscular blocking agents. These drugs were avoided for anaesthesia which was uneventful in all patients.

We conclude that patients who have severe reactions during anaesthesia which might be allergic should undergo skin testing. There was no significant difference in the reliability of diagnostic yield of intradermal or prick testing, and the choice of test could be based on other factors such as age of the patient, cost, ease of performance, unreliability of prick testing with propofol, lack of data on reliability of prick testing with time and outcome of subsequent anaesthesia in allergic patients when drug choice is based on prick testing. If the results of either test is negative or equivocal, intradermal and RIA testing should be performed. Where there are conflicting results all drugs which give positive tests by either method should be avoided.

The results of skin testing should be communicated in a letter stating drugs given, what happened, results and conclusions. The results of subsequent anaesthesia should be documented in the patient's letter and the file letter.

In reactions to neuromuscular blocking agents, the results agreed better for detecting the drug responsible for a reaction than determining cross sensitivity to other neuromuscular blocking drugs. It is sensible to suggest avoiding all neuromuscular blocking agents that may be positive as cross sensitivity occurs in 60% of patients.[16 22]

Safe subsequent anaesthesia is usual but not guaranteed when patients, who have had adverse reactions which may be allergic, receive drugs suggested to be safe on the basis of skin tests and history.

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British Journal of Anaesthesia 1997; 79: 64–67

Plasma dilution and the rate of infusion of Ringer's solution

R. G. HAHN AND C. SVENSÉN

Summary

Changes in the volume of the fluid space expanded by i.v. infusion of Ringer's acetate solution have been analysed recently using mathematical models. Data obtained by such analyses allow simulation of the dilution of the plasma volume during infusion of the solution at different rates. To obtain basic kinetic data for such simulations, the plasma dilution–time curves were measured during and after i.v. infusion of Ringer's solution 25 ml kg^{-1} over 30 min in 15 healthy male volunteers (mean age 31 yr) and over 30, 45 and 80 min in six females (mean age 32 yr). Based on these experiments, nomograms were constructed from which the rate of infusion of Ringer's solution and the infusion time required to obtain a defined plasma dilution in both males and females can be estimated together with the infusion rate needed to maintain the dilution at the level reached. (*Br. J. Anaesth.* 1997; **79**: 64–67).

Key words
Fluids, i.v. Fluid therapy. Fluid balance. Blood, haemodilution. Model, pharmacokinetic.

I.v. volume loading is frequently carried out by anaesthetists. The fluid load is usually given at a high rate to prevent circulatory instability before induction of spinal and extradural anaesthesia. Many anaesthetists also give a fluid load before general anaesthesia. However, the infusion rate required to rapidly expand the blood volume to a predetermined degree is largely unknown.

We have used a recently developed pharmacokinetic model adapted for body fluid spaces[1 2] to simulate the infusion rates required to effectively obtain and maintain a defined dilution of the plasma volume with Ringer's solution in healthy males and females. Our purpose was to open up the possibility of optimizing i.v. fluid therapy in clinical practice by setting a predetermined dilution of the plasma volume as the therapeutic goal. Volume expansion is the product of this dilution and baseline plasma volume. The kinetic data required for the simulations were obtained from volunteer experiments in which Ringer's's acetate solution was infused i.v.

Subjects and methods

MALE VOLUNTEERS

We studied 15 healthy men, aged 25–36 yr (mean 31 yr), weighing 65–100 kg (mean 78 kg). The study was approved by the local Ethics Committee and informed consent of all subjects was obtained.

Ringer's acetate solution 25 ml kg^{-1} (Pharmacia, Uppsala, Sweden) was given at a constant rate over 30 min via one or several infusion pumps (IVAC 560, San Diego, CA, USA). The ionic content of this solution is (in mmol $litre^{-1}$): Na^+ 130, K^+ 4, Ca^{2+} 2, Mg^{2+} 1, acetate 30 and Cl^- 110. Before any fluid was given, a cannula was placed in the cubital vein of each arm for blood sampling and infusion of fluid.

Venous blood was collected every 5 min for 3 h and blood haemoglobin concentration was measured using a Technicon H 2 (Bayer, Tarrytown, NY, USA) with a coefficient of variation of 1.3%. The first sample was obtained in duplicate and the mean value was used in calculations.

FEMALE VOLUNTEERS

Six female volunteers, aged 23–46 yr (mean 32 yr), body weight 50–75 kg (mean 60 kg) received 24 infusions of Ringer's solution. Under the same basic conditions as in the males, the volunteers were given, in random order and at intervals of at least 1 day, 25 ml kg^{-1} of this fluid over 30, 45 and 80 min.

Samples for measuring blood haemoglobin concentration on a Coulter Counter STKS (Counter Electronics, Hialeah, Fla., USA) were obtained from the venous cannula not used for infusion, before infusion, every 10 min during infusion and at 0, 5, 10, 15, 20, 25, 30, 60, 80, 100 and 120 min after infusion. The first haemoglobin sample in the series was obtained in duplicate and the mean was used in calculations.

In females, Ringer's solution was also infused very rapidly (100 ml min^{-1} over 15 min). However, these results were not used as the infusions caused symptoms, and therefore could not be used clinically. The results also differed from those at the slower infusion rates, which indicates that a different state exists when Ringer's solution is infused very rapidly. Details of these experiments are given elsewhere.[2]

ROBERT G. HAHN, MD, PHD, CHRISTER SVENSÉN, MD, Karolinska Institute, Department of Anaesthesia, Soder Hospital, S-118 83 Stockholm, Sweden. Accepted for publication: March 25, 1997.

Correspondence to R. H.

DATA ANALYSIS

Data on haemoglobin concentrations were analysed according to the one-volume fluid space (VOFS1) model which assumes that the infused fluid is distributed in a single well-stirred body fluid space.[1] Fluid is infused at a constant rate (k_i) and enters the body fluid space having the volume (v), which changes as a result of fluid leaving the space at a basal rate (k_b) and at a controlled rate (k_r) proportional to the deviation from the target value (V). Based on these assumptions, the following equation describes the volume change of the body fluid space expanded by the infusion:

$$dv/dt = k_i - k_b - k_r\,(v - V)/V$$

During (d) and after (a) infusion, the solution to this differential equation is:

$$w_d\,(t) = [(k_i - k_b)/k_r]\,(1 - e^{-k_r t/V}),\ 0 \leqslant t \leqslant t_1$$

$$w_a\,(t) = [-k_b/k_r]\,(1 - e^{-k_r (t-t_1)/V}) + w_d\,(t_1)\,e^{-k_r (t-t_1)/V},\ t_1 \leqslant t \leqslant \infty$$

where $w(t)$ is the dilution $(v(t) - V)/V$.

The random search method was chosen for the least-squares fitting procedure to obtain the best estimates of the unknown variables in the model (V and k_r), whereas k_b (basal fluid loss) was set to 1 ml min^{-1}.

Plasma dilution over time was simulated by setting these variables to the mean values for the respective groups of volunteers studied. For males, V was 6.61 litre (95% confidence interval 5.34–7.89 litre) and k_r 148 (95–201) ml min^{-1}. For females, we used 4.09 (3.44–4.74) litre and 111 (79–142) ml min^{-1}, respectively.

Simulations were performed in two steps, using Matlab version 4.2 (Math Works, Notich, MA, USA). The first step studied the infusion rate and infusion time required to obtain a definitive plasma dilution. The purpose of the second step was to maintain the dilution already obtained at a steady-state level (fig. 1). The required infusion rate is then dependent on the mode by which the infusion was given initially.

A two-volume fluid space model (VOFS2) has also been developed. In that model, the rate of volume equilibration between a primary and secondary fluid space is proportional to the difference in the relative deviation from the target value. Fitting the dilution–time curves to both VOFS1 and VOFS2 sometimes indicates that the latter model significantly reduces the mean square error. In particular, this occurs when urinary excretion in response to infusion is small.[2] Only VOFS1 is used here because it is difficult to know, in the clinical setting, for which patient VOFS2 is statistically justified. However, we undertook simulations also with VOFS2 in order to evaluate the magnitude of the error inflicted by the fact that some infusions are described better by the two-volume model.

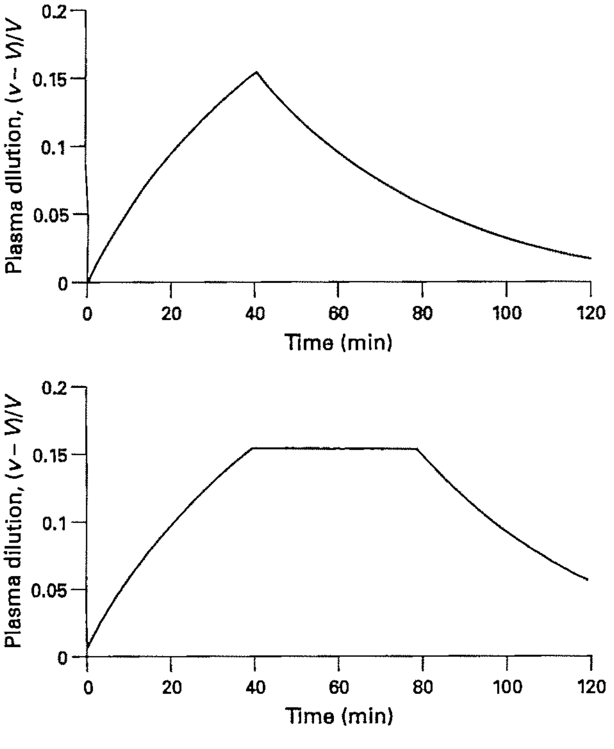

Figure 1 Examples of simulated plasma dilution–time curves in males performed in two steps, with step one (top), followed by step two where steady state is maintained (bottom). Ringer's solution is first given at a rate of 40 ml min^{-1} over 40 min and then discontinued. In step two, dilution is maintained using an infusion rate of 25 ml min^{-1}.

Results

The nomograms for men and women are shown in figures 2 and 3, respectively. In both cases, the first part of the fluid loading phase, when plasma dilution increased, was obtained from the left half of the nomogram. When the appropriate dilution is found, we trace the horizontal to the right half of the figure (along the same infusion rate line) to the line corresponding to the infusion time used. Thereafter, the steady-state infusion rate is given by the vertical correlation.

Consider that a male patient receives an infusion of Ringer's solution at a rate of 30 ml min^{-1} for 30 min (900 ml), after which a steady-state dilution is desired. The left nomogram indicates that dilution of plasma volume is close to 10%. The infusion rate that leads to a steady state is 15 ml min^{-1} and is given in the right half of the nomogram.

An example of how dilution of plasma volume by 15% can be found and maintained is shown in figure 1.

The nomograms were based on the VOFS1 model despite the fact that VOFS2 was statistically justified in 10 of the 15 experiments in males and in eight of the 24 experiments in females. In males, however, the times required to reach any target dilution when VOFS2 was applied differed by only ±2 min from those indicated by our nomogram. This difference was somewhat greater in females. With VOFS2, a plasma dilution of 5–15% was reached 2–5 min faster than that indicated by our nomogram. At the extreme, this difference amounted to 7–15 min when

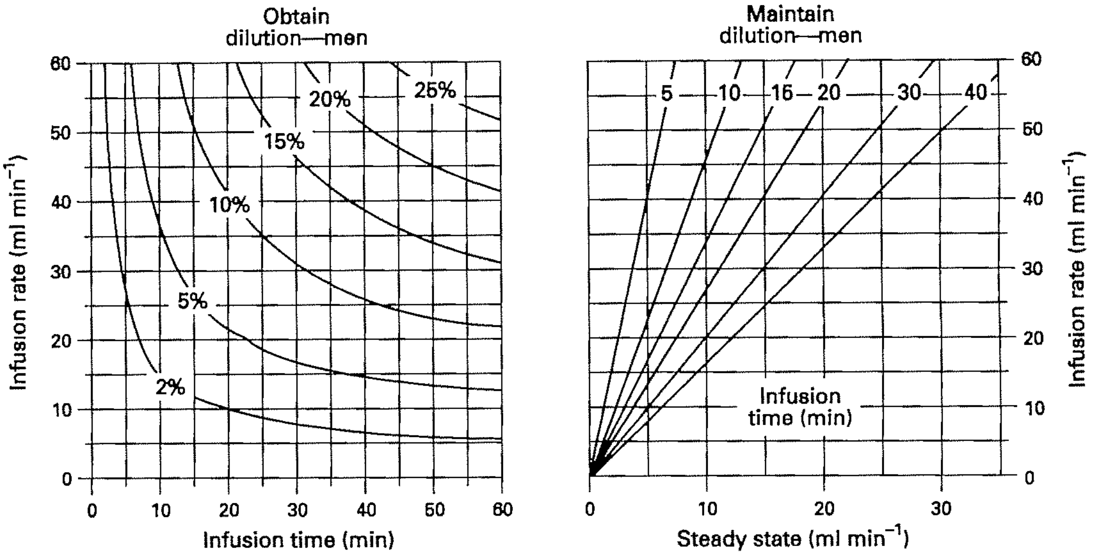

Figure 2 Nomograms for men showing the relationship between infusion rate and infusion time (left) and where the infusion rate required to maintain a steady-state dilution during a subsequent phase can be estimated by entering the initial infusion rate and infusion time used during the first phase (right).

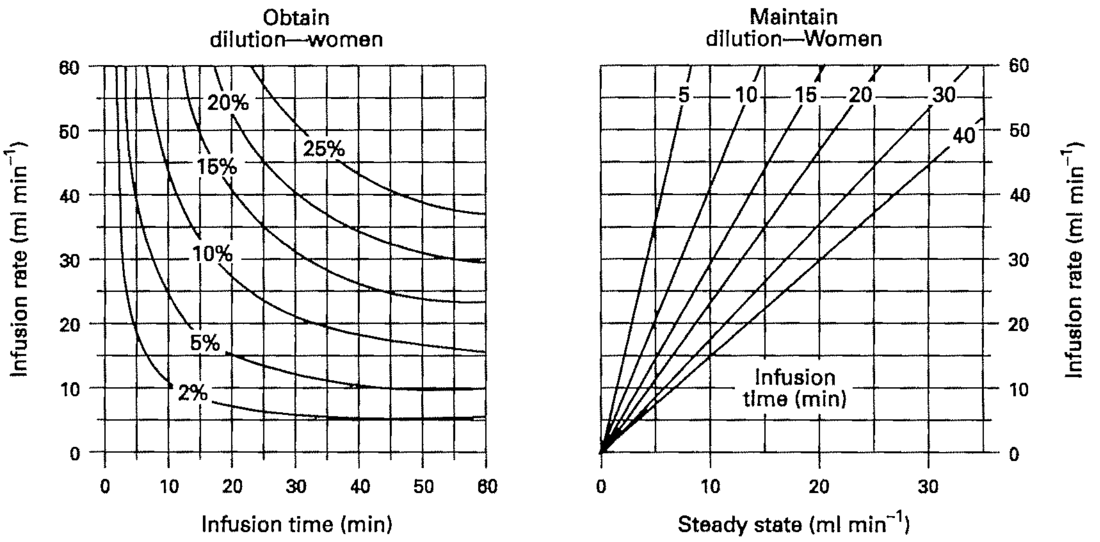

Figure 3 Same nomograms for women as those described for men in figure 2.

a low infusion rate was used to obtain a dilution of 20–25%.

Discussion

The purpose of carrying out fluid loading with Ringer's solution is to increase plasma volume by haemodilution. A defined fluid load is usually given over a specific time without an end-point being specified. We suggest that dilution of blood would be a suitable end-point as the volume expansion effect of the fluid is believed to be an important therapeutic goal. We have outlined the possibilities and limitations of this practice in an experimental situation. The nomograms we have constructed allow estimation of the infusion rate and time required to both obtain and maintain a defined dilution of plasma volume. They show how alternative fluid regimens can be found, all of which lead to the same defined dilution of plasma volume.

Although the nomograms quantify what the anaesthetist intuitively knows and does, the computer simulations made us realize that marked haemodilution is difficult to obtain in healthy awake humans. For example, the infusion rate must be at least 50 ml min^{-1} in a young man to yield a plasma dilution of 20%, which corresponds to an increase in blood volume of approximately 10%. Even at this high rate, the infusion has to continue for 40 min (and requires 2000 ml of fluid) to yield the desired dilution. In contrast, an infusion rate below 40 ml min^{-1} is not capable of diluting plasma volume by 20%, regardless of how long the infusion is continued. When fluid is infused at a high rate, it does not matter if the simulation is based on VOFS1 or VOFS2.

The difficulty in achieving pronounced haemodilution can be explained in part by rapid elimination of fluid. In the volume kinetic model, urinary excretion is proportional to plasma dilution, an assumption which receives support from the overall good agreement between measured urine volume and model-predicted urinary excretion.[2] Furthermore, compliance of the vascular system for volume expansion may prevent excessive haemodilution. When the rate of infusion of Ringer's solution is increased to 100 ml min^{-1}, haemodilution no longer increases. At this point, compliance is probably lower in the circulation than in the interstitial fluid space, and further infused fluid accumulates there. In our model, such accumulation of fluid is noted as an increase in the expandable fluid space (V). One should note, however, that haemodilution increases further if the patient's vascular status is changed, such as by extradural anaesthesia[3] or blood loss.[4] Therefore, the use of the nomograms derived in this study should be restricted to volume loading carried out before anaesthesia is induced. Furthermore, the volume kinetic data should not be extended to infusion rates higher than those used here.

The amount of fluid required for carrying out a fluid load can be estimated readily from the nomograms. Such calculations show that a fast infusion is more effective than a slow one. Imagine we wish to increase plasma volume by 10%, which corresponds to an increase in blood volume of 5%. In males, this can be achieved by infusing Ringer's solution at a rate of either 50 ml min^{-1} for 15 min (750 ml) or 25 ml min^{-1} for 45 min (1125 ml). The second infusion regimen requires 50% more fluid than the first despite the fact that the same dilution is obtained.

Nomograms were constructed for males and females separately as there seems to be sex-related differences in volume kinetics. Body weight and elimination rate constant (k_r) for Ringer's solution were 30% higher in males than in females and the size of the expandable fluid space (V) was 60% higher. These differences explain why marked dilution requires much higher infusion rates in men. Modest degrees of dilution, however, can be obtained by almost the same infusion rates as in women. The right parts of the nomograms ("maintain" dilution) are also similar for males and females, but one must remember that most infusion rates result in more pronounced dilution of plasma volume when Ringer's acetate is given to females.

The difference in V between the sexes can probably be explained by the larger body weight and greater percentage of water in the extracellular space, which amounts to 200 ml kg^{-1} of body weight in men compared with 150 ml kg^{-1} in females.[5] It is important to note, however, that our nomograms are not based on the size of the extracellular space but on the body fluid space that is actually expanded by Ringer's solution (V). This fluid space is different from the volume in which the same fluid is distributed and usually amounts to about twice the plasma volume. The concept of an expandable fluid space is relevant to emergency medicine, trauma care, anaesthesia and surgery, as V indicates hydration of the body resulting from i.v. fluid therapy.

Acknowledgement

We thank Associate Professor Lennart Edsberg, Department of Numerical Analysis and Computing Science, Royal Institute of Technology, Stockholm, Sweden, for designing the computer programs used in this study.

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British Journal of Anaesthesia 1997; 79: 68–77

LABORATORY INVESTIGATIONS

Beneficial effect of concomitant administration of isoflurane and nicorandil

V. Piriou, S. Ross, D. Pigott, R. Evans and P. Foex

Summary

In common with halogenated anaesthetics, nicorandil, a new K_{ATP} channel opener, has been shown to have cardioprotective and vasodilator effects. Recent studies have also suggested that the vasodilator and protective effects of halogenated anaesthetics are mediated partly via K_{ATP} channel opening. This study examined the effects of concurrent administration of nicorandil and isoflurane on haemodynamic state and ventricular function before, during and after 15 min of ischaemia. We studied left ventricular function in 40 anaesthetized rabbits using ultrasonomicrometry. Measurements were obtained before, during and after 15 min of regional ischaemia. Regional ventricular function was assessed in terms of systolic shortening (SS%) and preload recruitable work area (PRWA, the area beneath the regional stroke work *vs* end-diastolic length relationship) during reperfusion. Four groups were studied: group F (n=10) received a bolus dose of fentanyl 100 μg kg^{-1} and then 400 μg kg^{-1} h^{-1} throughout; group I (n=10) received 2.05% end-tidal concentration of isoflurane (1 MAC); group FN (n=10) received fentanyl, a bolus does of nicorandil 100 μg kg^{-1} and then 25 μg kg^{-1} min^{-1}, 15 min before occlusion; and group IN (n=10) received isoflurane and nicorandil. Isoflurane decreased left ventricular systolic pressure and ventricular contractility (+dP/d$t$max, slope of preload recruitable stroke work, and SS%). Nicorandil increased +dP/d$t$max in group FN. Post-ischaemic regional left ventricular contractility in group I did not differ from that in group F, however, groups receiving nicorandil recovered to a greater extent. Group IN showed better recovery compared with all other groups when ventricular contractility was assessed by PRWA normalized to pre-occlusion values (mean 99.3 (SEM 10.5) % *vs* 73.4 (7.5) %, 50.2 (5.8) % and 52.4 (3.7) % at 120 min reperfusion in groups FN, I and F, respectively). Tissue ATP and lactate contents did not differ between groups. We conclude that concurrent administration of nicorandil and isoflurane enhanced post-ischaemic recovery compared with isoflurane anaesthesia or nicorandil and fentanyl administration. (*Br. J. Anaesth.* 1997; **79**: 68–77).

Key words
Anaesthetics volatile, isoflurane. Heart, myocardial function. Pharmacology, nicorandil. Heart, nicorandil. Rabbit.

Nicorandil, a nicotidamide ester, is a potassium channel opener used in clinical practice for antianginal therapy.[1] This drug exhibits several actions, including vasodilatation, mediated by both nitrate radical and opening of K_{ATP} channels, and a cardioprotective effect, attributed mainly to opening of K_{ATP} channels.[2 3]

Isoflurane is a vasodilator and also a cardiodepressant and protective agent.[4] Recent investigations have shown that isoflurane-induced coronary vasodilatation[5] and its cardioprotective effect[6] are antagonized by glibenclamide, and therefore may be mediated partly by K_{ATP} channels.

With the possibility that the number of angina patients on long-term nicorandil treatment undergoing surgery and general anaesthesia will increase in the future, this study was designed to investigate the potential effects of concurrent administration of isoflurane with nicorandil and of fentanyl with nicorandil. Haemodynamic state and regional myocardial function before ischaemia, and the time course of functional regional recovery after 15 min of regional ischaemia were studied in an anaesthetized, open chest rabbit model.

Materials and methods

SURGICAL PREPARATION OF ANIMALS

The study conformed to UK Animals Acts (Scientific Procedures, 1986). We studied 73 New Zealand White rabbits of both sexes (2.5–3.5 kg) premedicated with xylazine 1 mg kg^{-1} i.m. and anaesthetized with ketamine HCl 75 mg kg^{-1} i.m. Adequate depth of anaesthesia was ensured before any surgical procedure by absence of pedal and palpebral reflexes. The marginal ear vein was cannulated (20-gauge cannula) for administration of fluids (hetastarch 3 ml kg h^{-1}) and drugs. The central ear artery was also cannulated (18-gauge cannula) and connected to a pressure

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Vincent Piriou, MD, Hôpital Cardio-Vasculaire Louis Pradel, Département d'Anesthésie Réanimation, B16, 28 Avenue Doyen Lépine, 69 500 Lyon Bron, France. Sean Ross, MSC, David Pigott, MB, CHB, Rhys Evans, MD, DPHIL, Pierre Foex, MD, DPHIL, Nuffield Department of Anaesthetics, The Radcliffe Infirmary, Oxford OX2 6HE. Accepted for publication: February 26, 1997.

Correspondence to V. P.

transducer (Druck Ltd, Groby, Leicester, UK) for measurement of arterial pressure during surgery. All catheters were flushed with heparinized saline 10 u. ml^{-1} to prevent clotting during the experiment. A tracheotomy was performed (tracheal tube size 4 mm od) and the lungs of the rabbits were ventilated mechanically (Servo ventilator 900B, Siemens-Elema, Sweden) with 100% oxygen. Tidal volume was set at 15 ml kg^{-1} and ventilatory frequency at 35 bpm. Ventilation was adjusted to maintain $P\text{CO}_2$ in the physiological range. End-tidal gas concentrations were measured continuously (gas analyser M1025A, Hewlett Packard, Bracknell, UK). Body temperature was recorded using the thermistor of a 7F pulmonary artery catheter (Swan-Ganz, American Edwards Laboratories, Anasco, Puerto Rico) inserted orally into the oesophagus and maintained at 39.0–40.5 °C. Limb lead II of the electrocardiogram was monitored continuously using subcutaneous needle electrodes. Anaesthesia was maintained with a bolus dose of fentanyl 100 μg kg^{-1} followed by an infusion of 400 μg kg^{-1} h^{-1} during surgery and the stabilization periods. The heart was exposed via a left thoracotomy and suspended in a pericardial cradle. A 5-0 Dexon suture was passed around the major marginal branch of the left coronary artery approximately halfway between the apex and base and the suture ends threaded through a small vinyl tube to make a coronary snare. Where possible we tried to avoid snaring coronary veins but in some experiments this was not possible. A thin piece of rubber tubing was placed around the inferior vena cava to perform caval occlusions. Pressure in the left ventricle was measured by inserting a 16-gauge cannula into the apex of the left ventricle and connecting this to a micromanometer-tipped 8F catheter (Millar, Houston, TX, USA) through a tight adapter. This device was compared, in our laboratory, during *in vivo* simultaneous pressure measurements with an 8F micromanometer-tipped catheter placed directly in the cavity of the left ventricle. The time lag between the two devices did not exceed 2 ms and the differences in pressure values were <1%. *In vitro* measurements showed an undamped natural frequency of 66.6 Hz and a damping coefficient of 0.141. This 16-gauge cannula was used to minimize impairment in regional myocardial function. Two piezoelectric crystals (0.8 mm diameter, Triton, San Diego, CA, USA) for ultrasonic measurement of segmental lengths were implanted in the endocardium in the apical region supplied by the snared marginal coronary artery parallel to the minor axis. These were implanted approximately 8 mm apart through epicardial stab wounds. At the end of the experiment the heart was excised rapidly and tissue samples obtained from the non-ischaemic region (above the coronary snare) and the ischaemic region (between the pair of crystals). These samples were frozen rapidly in a Wollenberger clamp cooled in liquid nitrogen and stored in liquid nitrogen for analysis of adenine nucleotides and lactate content.

MEASUREMENT OF TISSUE NUCLEOTIDES AND LACTATE CONCENTRATION

The frozen tissue samples were ground in liquid nitrogen and extracted with perchloric acid (6% w/v). The neutralized extracts were assayed for ATP,[7] ADP,[8] AMP[8] and lactate[9] using standard enzymatic techniques with a spectrophotometer (Lambda 3 UV/VIS spectrophotometer, Perkin Elmer Ltd, Beaconsfield, Bucks, UK).

Energy charge potential was calculated as follow[10]:

$$\frac{[\text{ATP}]+0.5[\text{ADP}]}{[\text{ATP}]+[\text{ADP}]+[\text{AMP}]}$$

STUDY PROCEDURE

Four groups of animals were studied (fig. 1) and all experiments were performed randomly. In all groups after surgery there was a stabilization period of 30 min, after which baseline measurements were obtained under fentanyl anaesthesia. After baseline measurements, recordings were obtained at 30, 45 and 60 min. The measurement at 60 min was taken as the pre-occlusion value used for normalization of contractility indices. One hour after baseline measurements, regional ischaemia was imposed for 15 min, followed by 120 min of reperfusion. During ischaemia, measurements were obtained at 5 and 15 min and during reperfusion at 5, 10, 15, 30, 60, 90 and 120 min.

In all groups, surgery and baseline measurements were performed under fentanyl anaesthesia. In the fentanyl group (group F, n=10), fentanyl was continued throughout the experiment. In the isoflurane group (group I, n=10) infusion of fentanyl was stopped after baseline measurements and 1 MAC of

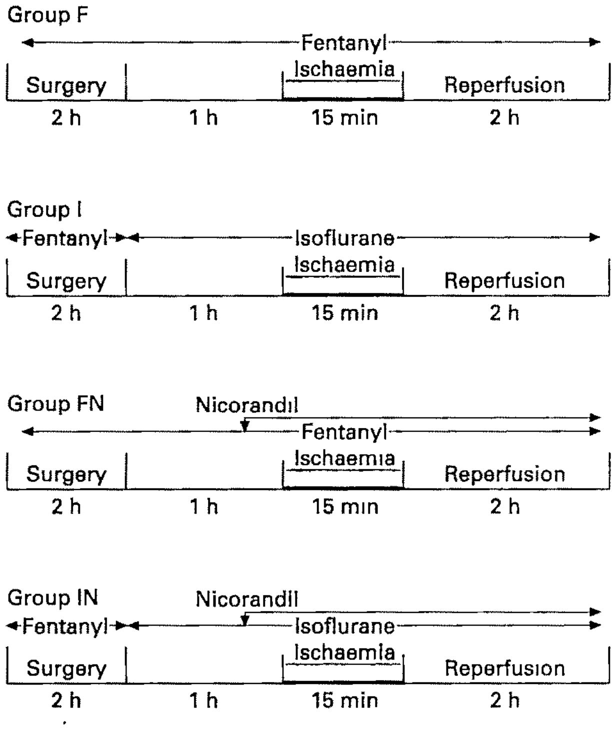

Figure 1 Study design.

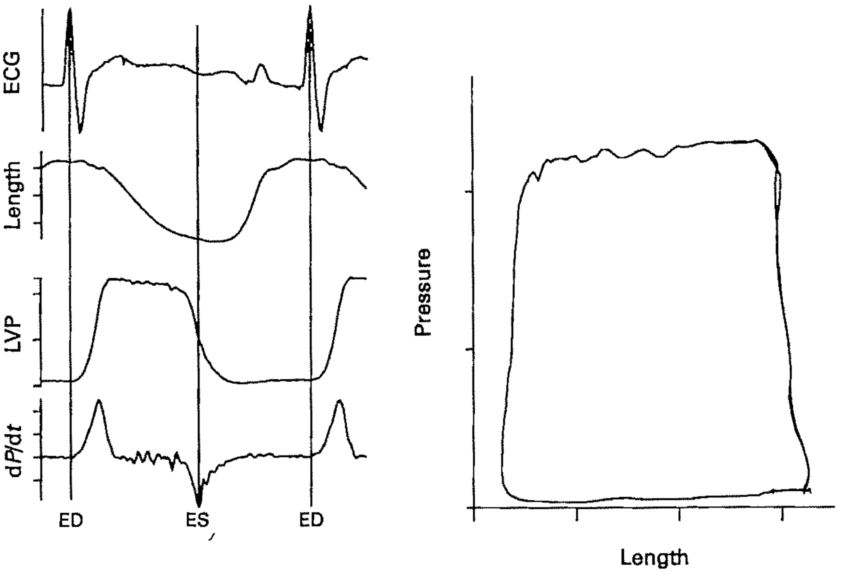

Figure 2 Signals obtained in one experiment before ischaemia. Left: ECG, apical length, left ventricular pressure (LVP) and d*P*/d*t*. The single cardiac beat is delineated by two end-diastolic lines (ED). End-systole (ES) was defined at peak negative d*P*/d*t*. Right: typical pressure–length loops.

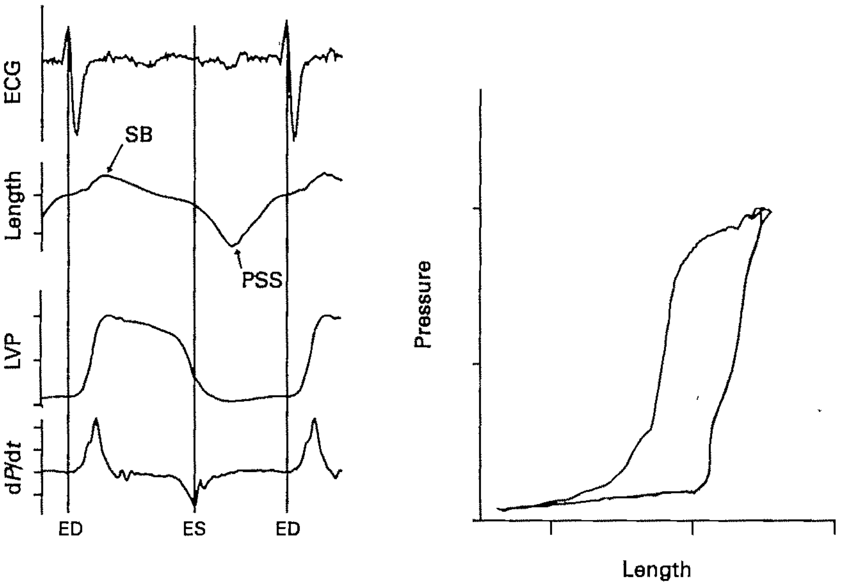

Figure 3 Signals obtained in one experiment during ischaemia. Left: ECG, apical length, left ventricular pressure (LVP) and d*P*/d*t*. The single cardiac beat is delineated by two end-diastolic lines (ED). End-systole (ES) was defined at peak negative d*P*/d*t*. Ischaemic length signal displays post-systolic shortening (PSS) and systolic bulging (SB). Right: typical pressure–length loops. The ischaemic pressure–length loop leans to the right.

isoflurane (2.05% end-tidal concentration)[11] introduced and continued for the duration of the experiment. In the fentanyl and nicorandil group (group FN, $n=10$) infusion of fentanyl was continued throughout the experiment and a bolus does of nicorandil 100 μg kg^{-1} followed by infusion of 25 μg kg^{-1} min^{-1} were started 15 min before coronary occlusion and continued for the duration of the experiment. In the isoflurane and nicorandil group (group IN, $n=10$) infusion of fentanyl was stopped after baseline measurements and 1 MAC of isoflurane introduced and continued for the duration of the experiment. A bolus dose of nicorandil 100 μg kg^{-1} followed by infusion of 25 μg kg^{-1} min^{-1} were started 15 min before coronary occlusion and continued for the duration of the experiment.

To produce ischaemia, the coronary snare was tightened by pulling the silk through the tubing. A bolus dose of lignocaine 0.7 mg kg^{-1} was infused just before coronary occlusion to prevent ventricular arrhythmias during ischaemia and reperfusion. Ischaemia was confirmed by changes in the shape of the pressure–length loop (reduction in systolic shortening, increase in post-systolic shortening and/or systolic bulging) (figs 2 and 3). Visually, myocardial ischaemia was confirmed by the appearance of regional myocardial surface cyanosis distal to the snare, and akinesia or bulging in this area. Experiments where these changes did not occur were discarded ($n=8$). After 15 min, the snare was released and reperfusion begun for a period of 2 h. Reperfusion was confirmed by changes in the pressure–length loop (increase in systolic shortening, reductions in post-systolic shortening and systolic bulging). Visually, reperfusion was confirmed by the appearance of hyperaemia. Animals that did not exhibit return of flow and change in ischaemic loop shape were excluded ($n=5$).

Measurements consisted of (1) steady state, and (2) caval occlusion obtained by pulling on the rubber tubing around the vena cava. Steady state variables were recorded for 5 s and caval occlusion for 15 s. All measurements were taken during expiratory apnoea to obtain an identical respiratory phase.

Nicorandil was dissolved in NaCl 0.9% (w/v). The dissolved nicorandil was infused in the marginal ear vein using an infusion pump.

DATA COLLECTION

ECG, pressures (central ear artery, left ventricular) and regional dimension signals were converted using an analogue-to-digital converter (AT-MIO-16, National Instruments Corporation, Austin TX, USA), and displayed continuously on an IBM AT personal computer using the real-time mode of software designed in this department. Data were sampled at a frequency of 500 Hz and stored on the hard disk. Pressure–length loops were displayed continuously on an oscilloscope.

DATA ANALYSIS

Data analysis was performed on an IBM AT personal computer using the play back mode of the above mentioned software. Peak positive and peak negative left ventricular dP/dt were obtained by electronic differentiation of the left ventricular pressure signal. End-diastole was defined as the first upward (positive) deflection of the left ventricular dP/dt signal. End-systole was defined as occurring at peak negative dP/dt.[12]

Length measurements were normalized to an initial value of end-diastolic length of 10 mm at control. The following definitions were used to quantify regional wall motion: EDL=end-diastolic length; ESL=end-systolic length; *l*max=maximum length during systole; *l*min=minimum segmental length during diastole. Systolic shortening fraction (%SS), systolic bulging (%SB) and post-systolic shortening (%PSS) were defined as follows:

$$\%SS = (EDL-ESL)/EDL \times 100$$
$$\%SB = (l\text{max}-EDL)/EDL \times 100$$
$$\%PSS = (ESL-l\text{min})/ESL \times 100$$

Systolic shortening was expressed in absolute values and as a percentage of pre-occlusion values to assess functional recovery during reperfusion. Area under the curve of systolic shortening *vs* time was also calculated during the reperfusion period.

Preload recruitable work area (PRWA) was calculated from the method devised by Glower and colleagues[13]; segmental stroke work (SW) was calculated by electronic integration of left ventricular pressure (P) and segmental length over the entire cardiac cycle:

$$SW = \int P \times dl$$

SW and end-diastolic segment length (EDL) were fitted using linear regression to the equation:

$$SW = Msw\ (EDL - Lw)$$

where Msw=slope and Lw=x-intercept.

PRWA was calculated from the equation:

$$PRWA = \frac{Msw}{2}(1.2Lwmax - Lw)^2$$

where Lwmax=maximal x-intercept value obtained for a given myocardial segment over the entire experiment.

PRWA was used to assess left ventricular function during the reperfusion period; values are expressed as a percentage of the pre-occlusion value. Area under the curve of PRWA *vs* time was also calculated during reperfusion.

STATISTICAL ANALYSIS

All values are expressed as mean (SEM). Statistical analyses were performed using two-way analysis of variance (ANOVA) with repeated measures on one factor. If ANOVA indicated significant differences between means, further comparisons were performed using Fisher's test. Statistical significance was assumed if $P<0.05$. Within-group comparisons were performed at times before ischaemia. Area under the curve and metabolic assays were analysed using one-way ANOVA followed by Fisher's test where appropriate.

Results

Of the 73 rabbits included in this study, 33 did not complete the experiment for the following reasons: death during surgery ($n=4$), crystals out of ischaemic area ($n=8$), lack of reperfusion after releasing the coronary snare ($n=5$), lethal ventricular fibrillation ($n=3$ in group F, $n=4$ in group I, $n=5$ in group FN and $n=4$ in group IN). Therefore, there were 10 animals in each group.

EFFECTS OF NICORANDIL OR ISOFLURANE, OR BOTH, BEFORE ISCHAEMIA

Isoflurane decreased left ventricular systolic pressure (LVSP) (73 (2) to 51 (1) mm Hg) while heart rate remained unchanged. Both $+dP/dt$max and $-dP/dt$min decreased with isoflurane suggesting a decrease in global contractility and lusitropy (table 1). Regional contractility was depressed in both groups receiving isoflurane, as indicated by the decrease in systolic shortening (27.3 (2.0) to 22.0 (1.4) % in group I and 28.7 (2.0) to 21.1 (1.8) % in group IN) and the slope of preload recruitable stroke work (Msw) (79.9 (11.1) to 42.7 (5.2) mm Hg in group I and 77.7 (10.4) to 43.0 (5.9) mm Hg in group IN) (table 2). Nicorandil infusion increased

Table 1 Global haemodynamic state before, during and after ischaemia (n=10 per group (mean (SEM)). F=Fentanyl group, I=isoflurane group, FN=fentanyl and nicorandil group, IN=isoflurane and nicorandil group. HR=Heart rate, LVSP=left ventricular systolic pressure, LVEDP=left ventricular end-diastolic pressure. $^{a}P<0.05$ compared with fentanyl group, $^{b}P<0.05$ compared with isoflurane group, $^{c}P<0$ 05 compared with fentanyl and nicorandil group, $^{d}P<0.05$ compared with isoflurane and nicorandil group. $^{*}P<0.05$ compared with previous time during pre-ischaemic period. Baseline measurements were recorded during fentanyl anaesthesia

	Pre-occlusion (min)				Occlusion (min)		Reperfusion (min)						
	Baseline	−30	−15	0	5	15	5	10	15	30	60	90	120
HR (beat min^{-1})													
F	231 (9)^{c}	232 (9)^{bcd}	227 (10)^{c}	226 (11)	227 (6)	235 (8)	233 (9)	230 (9)	227 (9)	221 (9)	235 (11)	241 (14)	241 (12)
I	212 (9)	208 (4)	209 (5)	216 (7)	215 (8)	227 (7)	224 (8)	223 (8)	224 (8)	231 (10)	239 (11)	235 (13)	240 (11)
FN	203 (7)	195 (8)	198 (10	220 (16)	226 (13)	241 (17)	230 (14)	247 (14)	243 (11)	242 (17)	248 (11)	244 (8)	258 (12)
IN	211 (7)	207 (8)	209 (7)	223 (7)	225 (8)	244 (12)	241 (12)	244 (12)	240 (13)	247 (15)	252 (14)	258 (14)	256 (11)
LVSP (mm Hg)													
F	72 (6)	70 (5)^{bd}	72 (4)^{bd}	75 (5)^{bd}	75 (6)^{bd}	74 (7)^{bd}	69 (5)^{bd}	73 (5)^{bd}	73 (5)^{bd}	72 (5)^{bd}	73 (5)^{bd}	71 (5)^{bd}	75 (4)^{bd}
I	73 (2)	51 (1)*	55 (2)	55 (1)	53 (3)	53 (2)	56 (3)	55 (2)	54 (2)	54 (2)	54 (2)	56 (2)	56 (2)
FN	68 (3)	71 (4)^{bd}	69 (4)^{bd}	68 (3)^{bd}	70 (4)^{bd}	70 (4)^{bd}	68 (2)^{bd}	71 (3)^{bd}	69 (3)^{bd}	70 (3)^{b}	72 (3)^{bd}	74 (3)^{bd}	71 (4)^{bd}
IN	73 (2)	51 (1)*	53 (2)	54 (3)	51 (3)	55 (3)	56 (3)	57 (3)	57 (3)	60 (4)	58 (3)	57 (3)	56 (3)
LVEDP (mm Hg)													
F	4.5 (0.9)	4.9 (1.0)	4.4 (0.8)	4.6 (0.8)	9.8 (1.6)	9.3 (1.6)	6.3 (1.3)	5 9 (0.9)	6.0 (1.0)	5.3 (1.0)	5.3 (0.9)	5.5 (1.0)	5.8 (1.0)
I	4.0 (0.7)	4.2 (0.5)	4.9 (0.4)	4.7 (0.5)	9.0 (0.8)	8.4 (0.9)	5.7 (0.6)	6.2 (0.7)	5.6 (0.6)	5.5 (0.5)	5.3 (0.5)	5.9 (0.6)	5.9 (0.8)
FN	3.4 (0.4)	3.7 (0.3)	3.6 (0.3)	3.6 (0.4)	8.8 (1.3)	9.6 (2.1)	7.3 (1.8)	6.3 (1.2)	5.9 (1.4)	5.8 (1.3)	5.4 (1.2)	5.6 (1.0)	6.0 (1.1)
IN	4.5 (0.5)	5.0 (0.4)	5.3 (0.4)	5.1 (0.5)	8.2 (0.8)	7.8 (0.8)	7.0 (0.9)	6.4 (0.6)	6.2 (0.5)	5.9 (0.4)	5.9 (0.5)	5.4 (0.5)	7.4 (1.5)
+dP/d$t$max (mm Hg s^{-1})													
F	3000 (318)	3321 (388)^{bd}	3628 (446)^{bd}	3670 (489)^{bd}	3173 (408)^{bd}	2961 (483)^{b}	2762 (410)^{bd}	2901 (403)^{bd}	2934 (329)^{bd}	3090 (337^{bd}	3421 (396)^{bd}	3034 (408)^{b}	3218 (361)^{bd}
I	3041 (123)	1557 (59)*	1644 (50)	1779 (66)	1689 (142)	1731 (131)	1612 (99)	1835 (130)	1754 (123)	1831 (137)	1819 (91)	1810 (108)	1758 (106)
FN	3164 (162)	3119 (168)^{bd}	3276 (293)^{bd}	3835 (307)^{bd*}	3551 (404)^{bd}	3484 (402)^{bd}	2801 (218)^{bd}	2887 (180)^{bd}	2962 (161)^{bd}	3287 (197)^{bd}	3844 (297)^{bd}	3884 (268)^{bd}	3549 (303)^{bd}
IN	3050 (171)	1419 (70)*	1452 (63)	1629 (128)	1687 (176)	2020 (220)	1940 (263)	2012 (287)	1986 (296)	2230 (403)	2418 (335)	2286 (346)	2148 (289)
−dP/d$t$min (mm Hg s^{-1})													
F	3423 (504)	3223 (394^{b})^{d}	3451 (347)^{bd}	3580 (414)^{bd}	3378 (474)^{bd}	3267 (512)^{bd}	3034 (369)^{bd}	3190 (377)^{bd}	3197 (366)^{bd}	3177 (409)^{bd}	3222 (367)^{bd}	3116 (436)^{bd}	3444 (356)^{bd}
I	3255 (189)	1551 (55)*	1742 (78)	1870 (68)	1633 (229)	1688 (203)	1754 (108)	1985 (203)	1816 (144)	1651 (115)	1720 (155)	1797 (164)	1790 (211)
FN	2999 (252)	3189 (298)^{bd}	3116 (376)^{bd}	2996 (252)^{bd}	2853 (288)^{bd}	2714 (259)^{b}	2661 (198)^{b}	2824 (210)^{bd}	2737 (180)^{bd}	2785 (212)^{b}	3106 (287)^{bd}	3335 (261)^{bd}	3110 (252)^{bd}
IN	3401 (153)	1557 (62)*	1658 (102)	1846 (234)	1498 (182)	1837 (229)	2012 (234)	1896 (208)	1830 (224)	1928 (369)	1947 (234)	1807 (269)	1775 (244)

Table 2 Regional indices of mechanical function before, during and after ischaemia (n=10 per group) (mean (SEM)). F=Fentanyl group, I=isoflurane group, FN=fentanyl and nicorandil group, IN=isoflurane and nicorandil group. EDL=End-diastolic length, SS=systolic shortening (actual values), Msw=slope of preload recruitable stroke work, PSS=post-systolic shortening and SB=systolic bulging. $^{a}P<0.05$ compared with fentanyl group, $^{b}P<0.05$ compared with isoflurane group, $^{c}P<0.05$ compared with fentanyl and nicorandil group. $^{d}P<0.05$ compared with isoflurane and nicorandil group, $^{*}P<0.05$ compared with previous time during pre-ischaemic period. Baseline measurements were recorded during fentanyl anaesthesia

	Pre-occlusion (min)				Occlusion (min)		Reperfusion (min)						
	Baseline	−30	−15	0	5	15	5	10	15	30	60	90	120
EDL (mm)													
F	10.0 (0.0)	10.0 (0.3)	10.1 (0.3)	10.1 (0.2)	11.2 (0.3)	11.1 (0.3)	10.4 (0.3)	10.9 (0.3)	10.9 (0.3	10.5 (0.2)	10.8 (0.3)	10.5 (0.2)	10.5 (0.1)
I	10.0 (0.0)	10.1 (0.3)	10.2 (0.3)	10.1 (0.3)	10.5 (0.3)	10.6 (0.3)	10.3 (0.3)	10.5 (0.2)	10.4 (0.2	9.3 (1.1)	10.3 (0.2)	10.3 (0.2)	10.4 (0.2)
FN	10.0 (0.0)	10.1 (0.2)	10.0 (0.2)	9.9 (0.2)	12.3 (0.5)^{abd}	12.1 (0.5)^{bd}	10.9 (0.5)	11.3 (0.6)	10.9 (0.2	11.0 (0.3)	10.6 (0.2)	10.6 (0.2)	10.7 (0.3)
IN	10.0 (0.0)	10.1 (0.1)	10.2 (0.2)	10.0 (0.2)	10.8 (0.3)	10.8 (0.3)	10.1 (0.2)	10.4 (0.3)	10.4 (0.3	10.4 (0.3)	10.1 (0.3)	10.1 (0.3)	10.1 (0.3)
SS (%)													
F	27.7 (2.5)	29.5 (3.0)^{d}	29.7 (3.0)	29.6 (3.2)^{bd}	−0.3 (1.8)	−0.8 (1.9)	12.6 (3.4)	11.7 (2.8)	12.6 (2.7	16.6 (2.4)	21.3 (3.3)	18.1 (2.6)	18.3 (2.9)
I	27.3 (2.0)	22.0 (1.4)*	22.2 (1.8)	21.5 (1.3)	−0.1 (1.3)	0.5 (1.3)	10.8 (1.2)	10.4 (1.2)	10.8 (1.5	12.3 (1.7)	13.9 (1.7)	13.8 (1.8)	13.0 (1.6)
FN	32.1 (3.6)	33.5 (4.0)^{bd}	33.0 (4.2)^{bd}	37.0 (4.0)^{bd}	3.2 (2.4)	0.7 (3.1)	18.1 (3.5)^{b}	18.2 (2.5)^{abd}	21.3 (2.3^{abd}	28.7 (2.6)^{abd}	31.4 (3.0)^{abd}	28.2 (2.6)^{abd}	28.7 (2.4)^{abd}
IN	28.7 (2.0)	21.1 (1.8)*	22.0 (1.6)	20.8 (1.8)	−0.8 (1.5)	−1.0 (1.3)	11.9 (1.4)	11.1 (1.7)	12.6 (1.8	17.4 (2.5)	19.2 (2.3)	18.6 (2.4)	18.3 (2.1)
Msw (mm Hg)													
F	80.9 (12.7)	84.9 (12.9)^{bd}	86.2 (17.0)^{bd}	95.5 (19.6)^{bd}	18.9 (3.3	18.1 (2.6)	49.1 (7.0)^{b}	60.6 (6.6)^{bd}	65.4 (7.7^{b}	74.9 (8.3)^{b}	82.1 (6.7)^{b}	81.3 (9.7)^{bd}	80.2 (10.8)^{bd}
I	79.9 (11.1)	42.7 (5.2)*	45.9 (6.5)	44.3 (8.2)	10.7 (1.3)	14.5 (3.2)	31.1 (2.9)	29.5 (1.7)	34.3 (2.6	40.7 (4.3)	49.4 (5.1)	47.2 (5.4)	47.9 (5.7)
FN	74.0 (6.2)	75.6 (7.2)^{bd}	74.5 (7.3)^{d}	83.0 (7.8)^{bd}	20.7 (4.3)^{bd}	22.8 (4.2)	51.3 (6.8)^{bd}	58.4 (4.2)^{bd}	60.0 (6.5^{b}	71.9 (8.6)^{b}	78.9 (6.9)^{b}	82.5 (9.2)^{bd}	73.4 (6.7)^{b}
IN	77.7 (10.4)	43.0 (5.9)*	40.8 (4.2)	44.3 (5.3)	10.6 (2.2)	13.9 (3.3)	34.9 (4.7)	38.6 (7.4)	50.4 (11.7	64.4 (11.4)	63.3 (8.1)	54.3 (6.6)	55.8 (4.8)
PSS (%)													
F	1.1 (0.6)	1.0 (0.6)	1.2 (0.6)	1.5 (0.7)	11.1 (2.3)	11.1 (2.5)	9.2 (2.1)	6.8 (1.9)	3.7 (1.5	3.3 (1.4)	3.3 (1.4)	4.2 (1.9)	4.5 (1.7)
I	0.4 (0.4)	0.9 (0.8)	1.1 (0.7)	1.4 (0.8)	8.1 (2.3)	7.9 (2.3)	5.9 (0.9)	4.7 (0.8)	3.4 (0.9	1.4 (0.6)	1.4 (0.8)	2.0. (1.0)	1.4 (0.9)
FN	1.0 (0.6)	1.0 (0.7)	1.5 (0.8)	0.7 (0.4)	9.2 (1.8)	8.2 (0.9)	9.5 (2.0)	7.8 (2.5)	5.5 (2.8	3.2 (1.6)	1.4 (1.2)	3.5 (2.3)	3.0 (2.0)
IN	4.0 (1.8)^{abc}	2.6 (1.9)	3.1 (1.9)	2.8 (2.2)	12.1 (2.3)	12.1 (2.8)	9.8 (1.3)	8.5 (1.8)	7.4 (2.1	4.2 (1.6)	4.3 (1.8)	4.1 (1.5)	3.8 (1.7)
SB (%)													
F	1.0 (0.6)	1.0 (0.3)	1.0 (0.3)	1.5 (0.4)^{b}	6.2 (1.5)	5.8 (1.6)	3.8 (1.5)	3.4 (1.2)	2.7 (0.9	2.5 (0.9)^{b}	1.1 (0.5)	2.2 (0.9)^{b}	2.1 (0.9)
I	0.5 (0.2)	0.4 (0.2)	0.2 (0.1)	0.2 (0.1)	4.6 (1.6)	4.5 (1.6)	1.5 (1.0)	1.5 (0.9)	1.0 (0.6	0.1 (0.1)	0.2 (0.1)	0.1 (0.1)	0.1 (0.1)
FN	1.3 (0.5)	1.6 (0.8)	1.5 (0.6)^{b}	0.9 (0.2)	4.9 (1.2)	4 2 (1.1)	3.6 (1.3)	2.1 (0.6)	2.2 (0.9	0.7 (0.3)	1.0 (0.5)	1.0 (0.4)	1.2 (1.1)
IN	2.2 (0.5)^{b}	1.5 (0.5)	1.2 (0.4)	1.6 (0.4)^{b}	4.4 (0.9)	4.7 (0.8)	3.7 (1.0)	3.3 (0.9)	2.7 (0.9	1.6 (0.9)	1.9 (0.8)^{b}	2.0 (0.8)^{b}	2.5 (0.9)

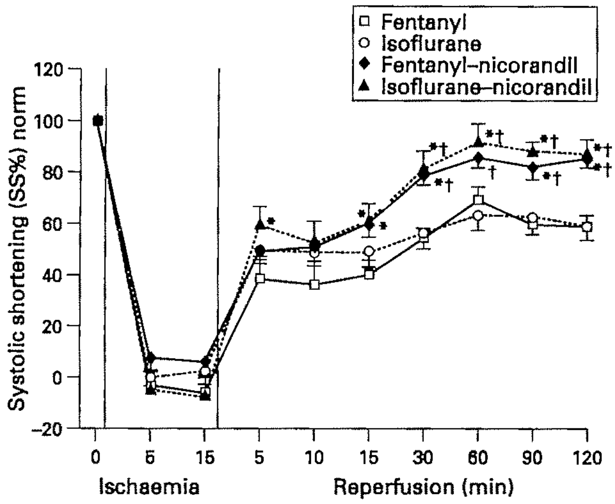

Figure 4 Changes in systolic shortening (SS%) normalized to pre-occlusion values during and after ischaemia for the four groups. *$P<0.05$ compared with fentanyl group, †$P<0.05$ compared with isoflurane group.

Table 3 Comparison of area under the curve between groups ($n=10$ per group) (mean (SEM)). F=Fentanyl group, I=isoflurane group, FN=fentanyl and nicorandil group and IN=isoflurane and nicorandil group. SS=Systolic shortening (normalized) and PRWA=preload recruitable work area (normalized). $^{a}P<0.05$ compared with fentanyl group, $^{b}P<0.05$ compared with isoflurane group, $^{c}P<0.05$ compared with fentanyl and nicorandil group

	Group			
	F	I	FN	IN
SS%	6766 (462)	6936 (658)	9206 (422)^{ab}	9 682 (559)^{ab}
PRWA%	5506 (417)	5639 (450)	8119 (499)^{ab}	10 896 (994)^{abc}

+d*P*/d*t*max in group FN (3276 (293) to 3835 (307) mm Hg s^{-1}). EDL and EDP remained unchanged with isoflurane or nicorandil, or both.

EFFECTS OF NICORANDIL OR ISOFLURANE, OR BOTH, AFTER ISCHAEMIA

Both groups receiving isoflurane exhibited lower LVSP, +d*P*/d*t*max and −d*P*/d*t*min than both groups receiving fentanyl. Nicorandil did not affect these variables (table 1). Table 2 shows the changes in systolic shortening expressed as absolute values; group FN displayed higher values than the three other groups, however, this group displayed higher pre-occlusion values than groups I and IN. Systolic shortening normalized to the pre-occlusion value exhibited higher values in both groups receiving nicorandil (fig. 4). This was confirmed by the area under the curve (table 3). PRWA (fig. 5) showed similar trends, but at variance with the previous indices there were significant differences between groups IN and FN (99.3 (10.5) and 73.4 (7.5) %, respectively, at 120 min reperfusion). This was confirmed by the area under the curve (table 3). The differences between groups became more obvious after 30 min of reperfusion.

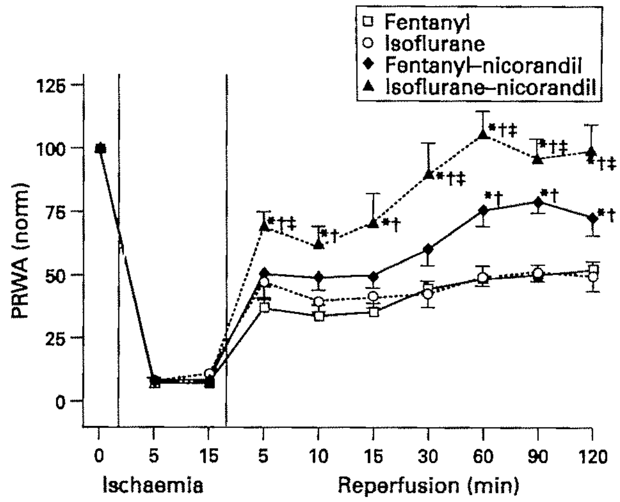

Figure 5 Changes in preload recruitable work area (PRWA) normalized to pre-occlusion values during and after ischaemia for the four groups. *$P<0.05$ compared with fentanyl group, †$P<0.05$ compared with isoflurane group, ‡$P<0.05$ compared with fentanyl–nicorandil group.

BIOCHEMICAL ANALYSIS

Tissue ATP concentrations were similar between groups; however ATP concentrations were decreased significantly in reperfused tissue (previously ischaemic region) compared with non-ischaemic areas in each group. Lactate and energy charge were not different between groups or within regions (table 4).

Table 4 ATP, lactate and energy charge levels in reperfused and non-ischaemic tissue (μmol g^{-1} wet weight). F=Fentanyl group, I=isoflurane group, FN=fentanyl and nicorandil group and IN=isoflurane and nicorandil group. *$P<0.05$ compared with non-ischaemic tissue

	Group ($n=10$ per group)			
	F	I	FN	IN
ATP				
Reperfused	1.175 (0.1521)*	1.252 (0.070)*	1.316 (0.129)*	1.404 (0.079)*
Non-ischaemic	2.154 (0.174)	2.323 (0.227)	2.153 (0.136)	2.541 (0.082)
Lactate				
Reperfused	4.518 (0.187)	4.051 (0.232)	4.605 (0.249)	4.088 (0.359)
Non-ischaemic	4.416 (0.305)	4.262 (0.249)	4.244 (0.2606)	4.056 (0.339)
Energy charge				
Reperfused	0.692 (0.0238)	0.669 (0.0172)	0.689 (0.0186)	0.703 (0.016)
Non-ischaemic	0.691 (0.0231)	0.690 (0.0267)	0.691 (0.0134)	0.744 (0.010)

Discussion

K_{ATP} channels are present in several tissues, including cardiac muscle and vascular smooth muscle. Their gating is metabolically dependent; a decrease in intracellular ATP or increase in ADP or protons may induce a K^+ outward current which hyperpolarizes the cell. Glibenclamide, a K_{ATP} channel blocker, increases basal coronary tone, suggesting that K_{ATP} channels play an important physiological role in coronary vasoregulation.[14] K_{ATP} channels have also been implicated in the cardioprotection produced by agents such as nicorandil[15] and isoflurane.[6 16]

Nicorandil is a K_{ATP} channel opener; it induces vasodilatation because of cell membrane hyperpolarization resulting in decreased calcium entry through T- and L-type calcium channels. Vasodilatation is also attributed to the presence of a nitrate radical. Small artery dilatation seems to be mediated by a K_{ATP} channel opening action and large artery dilatation mediated by a nitrate-like effect.[17] Experimental studies in dogs[18] have shown that nicorandil enhances cardiac function. This could be attributed to altered loading status,[19] increased coronary flow, or both.[20]

Isoflurane causes dose-related vasodilatation. Patch clamp studies have shown that it acts by suppressing calcium currents.[21] Recently, Cason, Shubayev and Hickey[5] demonstrated that isoflurane-induced coronary vasodilatation *in vivo* is antagonized by the K_{ATP} channel blocker glibenclamide and concluded that this vascular effect is mediated mainly by K_{ATP} channel modulation; similar results have been obtained with halothane.[22] To our knowledge, only one study has investigated the potential haemodynamic effects of the combination of nicorandil and isoflurane: Tanaka,[23] using 0.75% and 1.5% isoflurane in an open chest anaesthetized dog model investigated the global haemodynamic effects of bolus doses of nicorandil 100 $\mu g\ kg^{-1}$ and 300 $\mu g\ kg^{-1}$. They showed that the hypotensive effects of both nicorandil doses disappeared after 5 min at both isoflurane concentrations. Cardiac output was slightly increased during the first minute at both doses, as there was a transient decrease in vascular resistance.

The cardiodepressant properties of isoflurane are mediated by inhibition of trans-sarcolemmal calcium influx by T- and L-calcium voltage-dependent channels.[24] This results in decreased calcium availability for myocardial contraction. Contractile myofibrils also exhibit decreased calcium sensitivity. Compared with other halogenated anaesthetics, isoflurane seems to have less effect on the sarcoplasmic reticulum. In this study, isoflurane was set at 1 MAC (rabbit) end-tidal concentration, equivalent to 2.05%,[11] a dose that causes marked hypotension and cardiodepression in this model.

In our model, nicorandil showed no hypotensive effects 15 min after the bolus dose of 100 $\mu g\ kg^{-1}$ and continuous infusion of 25 $\mu g\ kg^{-1}\ min^{-1}$, with fentanyl or isoflurane anaesthesia. However, $+dP/dt$max was increased significantly after administration of nicorandil with fentanyl but not isoflurane anaesthesia, possibly because of the magnitude of induced vasodilatation and cardiodepression with isoflurane. Using a model similar to ours, Iwamoto and colleagues[15] showed a cardioprotective effect without hypotensive action with infusion of nicorandil 10 $\mu g\ kg^{-1}\ min^{-1}$.

Mechanisms underlying transient post-ischaemic myocardial dysfunction are still not fully understood. The more favoured causes are cytosolic calcium overloading ("calcium paradox"), formation of free radicals during reperfusion and decrease in myofibril sensitivity to calcium. During ischaemia, intracellular ATP decreases and ADP, lactate and acidosis increase in the cardiac myocyte. These intracellular metabolic alterations induce efflux of potassium ions through K_{ATP} channels shortening action potential duration. Contractility in ischaemic myocardium is reduced and metabolic demand decreases. The protective effects of nicorandil on stunned myocardium have been studied extensively in a chronically instrumented dog model[25] and in a pentobarbitone-anaesthetized open chest dog model.[2 3] These studies on stunned myocardium used similar doses of nicorandil as in this study. In these investigations myocardial function was assessed by regional systolic shortening (SS%). Several studies have also reported a decrease in infarct area after longer periods of ischaemia using nicorandil. The cardioprotective effect has been attributed to the dual properties of nicorandil: potassium channel opener[2] and vasodilator,[26] although the role of the latter is still debated. Compared with equi-hypotensive doses of nitrates, nicorandil showed improved recovery.[3] However, intracoronary infusion of nicorandil[26] and systemic infusion of aprikalim, a pure potassium channel opener, after ischaemia,[27] did not show a demonstrable beneficial effect. Other properties may be involved in the protective effect of nicorandil, including free radical scavenging activity[28] and antiplatelet aggregatory function.[29]

Halogenated anaesthetics also have cardioprotective properties. Both halothane and isoflurane have been shown to improve post-ischaemic recovery in several animal models[4 30–32] but the mechanisms remain unclear; decreased myocardial contractility and oxygen demand do not appear to play major roles.[33] Halogenated anaesthetics are more likely to exert their effects by decreasing the intracellular calcium transient, thereby protecting the heart against calcium overloading. The free radical scavenging properties of isoflurane[34 35] may also be involved. Kersten and colleagues[6] have recently shown that isoflurane-induced cardioprotection in stunning is partially blocked by glibenclamide in a chronic dog model, suggesting a role for K_{ATP} channels.

We have been unable to show a protective effect on myocardial recovery for isoflurane compared with fentanyl. The low perfusion pressure displayed by the groups receiving 1 MAC of isoflurane may have affected recovery, and coronary steal may have been induced,[36] although this phenomenon is still debated.[37] In our study, we demonstrated enhanced recovery from stunning in animals receiving both isoflurane and nicorandil. The group receiving isoflurane and nicorandil showed significant enhancement (+26%) in PRWA compared with the group receiving fentanyl and nicorandil. PRWA is a good index of systolic function in the post-ischaemic period; compared with systolic shortening, it is sensitive and relatively load independent.[13] By expressing contractility as systolic shortening in absolute values, the isoflurane and nicorandil group recovered less compared with the fentanyl and nicorandil group. This may be attributed to the cardiodepressive activity of isoflurane, as shown by the similar recovery when systolic shortening in the isoflurane group was normalized to a pre-occlusion value.

Our study demonstrated significant depletion in tissue ATP content in the previously ischaemic area in all groups; this was not, however, reflected in decreased energy charge in the same areas. Assessment of cellular energy status may include other indices not measured here, such as phosphorylation potential ([ATP]/[ADP]+Pi), phosphocreatine and glycogen contents. However, it is likely that turnover and flux rates of energy substrates and intermediary metabolites are more important than absolute concentrations. Another relevant factor in this context is compartmentation of metabolites between subcellular sites. Measurements of whole tissue concentrations cannot account for localization of energy substrates within different organelles. Indeed, it has been suggested that whole tissue myocardial ATP content is not related to functional recovery after ischaemia,[38 39] an observation confirmed by this report.

Tissue lactate concentrations were also unchanged after 2 h of reperfusion in all groups, confirming the metabolic integrity implied by the energy charge status and suggesting myocardial stunning with good biochemical recovery at 2 h of reperfusion rather than overt tissue infarction.

LIMITATIONS

Using this model we cannot state unequivocally if the differences in functional recovery were related to better functional recovery in stunned myocardium or to diminished infarct size. Weisel[40] suggested a time of 10–20 min for stunning in rabbits. We did not measure collateral circulation, but radiomicrosphere studies[41] have shown that collateral circulation in rabbits is poor (2%) compared with dogs (16%). This is one major advantage of using the rabbit model to study stunning. As we used an acute model, this study did not examine contractile function in reperfused areas after recovery from anaesthesia; a similar study with a chronic model would be necessary to establish the extent of recovery without anaesthesia. Our model did not allow us to measure coronary flow to determine if there was further enhancement of coronary flow with the combination of isoflurane and nicorandil, which may induce coronary steal. However, if this was the case recovery would be expected to be less in this group compared with the fentanyl and nicorandil group. Systolic pressures were very low in the isoflurane groups, however further experiments carried out in this department using 0.5 MAC of isoflurane have shown the same degree of contractile recovery with systolic pressures greater than 70 mm Hg (unpublished observations). Plasma concentrations of nicorandil were not measured, therefore we cannot be certain that plasma concentrations were stable during the experiment. Moreover, the cardiovascular system of the rabbit appears to be more sensitive to isoflurane. Consequently, caution must be exercised before relating this work to a clinical situation.

In summary, we have shown better recovery of stunned myocardium with the addition of nicorandil to isoflurane or fentanyl anaesthesia in acutely instrumented anaesthetized rabbits. The mechanisms underlying the benefits of the combination of isoflurane and nicorandil are unclear. Enhancement of the cardioprotection afforded by nicorandil and isoflurane may involve K_{ATP} channel opening.

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Effect of halothane on K^+ and carbachol stimulated [^{3}H]noradrenaline release and increased $[Ca^{2+}]_i$ in SH-SY5Y human neuroblastoma cells

R. ATCHESON, K. BJORNSTROM, R. A. HIRST, D. J. ROWBOTHAM AND D. G. LAMBERT

Summary

We have examined the effects of the volatile general anaesthetic agent, halothane, on K^+ and carbachol stimulated [^{3}H]noradrenaline release and associated increases in intracellular Ca^{2+} in a cultured human neuroblastoma cell line, SH-SY5Y. K^+ (but not carbachol) stimulated [^{3}H]noradrenaline release, and the increase in intracellular Ca^{2+} concentration was entirely extracellular Ca^{2+} dependent. Halothane produced a dose-dependent reduction in K^+ evoked release of [^{3}H]noradrenaline with significant inhibition (17%) occurring from 1.26 atm%. Basal and carbachol evoked release were unaffected. Halothane also produced a dose-dependent reduction in K^+ evoked increases (measured at the peak) in intracellular Ca^{2+} with significant inhibition (29%) occurring from 0.88 atm%. K^+ plateau, basal and carbachol evoked increases in intracellular Ca^{2+} were unaffected. These data suggest that halothane reduced Ca^{2+} entry through voltage-sensitive Ca^{2+} channels and implicate this important class of ion channel in the mechanism of anaesthesia. (*Br. J. Anaesth.* 1997; **79**: 78–83).

Key words
Anaesthetics volatile, halothane. Ions, ion channels, voltage-gated. Ions, calcium. Sympathetic nervous system, noradrenaline. Model, neuroblastoma cells. Theories of anaesthetic action, molecular.

Neurophysiological studies suggest that anaesthetic agents depress synaptic transmission by reducing neurotransmitter release with axonal conduction remaining relatively unaffected.[1–3] While there is good agreement that neurotransmission is reduced, the precise cellular mechanism(s) remains to be fully elucidated. At clinically relevant concentrations, anaesthetic agents (with the exception of ketamine) interact with $GABA_A$ receptors to increase Cl^- conductance and produce hyperpolarization, suggesting that this may be a common target site for all anaesthetic agents.[4,5] However, at variance with this hypothesis is the observation that some anaesthetics *inhibit* the release of GABA.[6,7] While the GABA hypothesis is extremely attractive, it is premature to discount other potential target site(s). One such target is the voltage-sensitive Ca^{2+} channel and there has been much debate as to its importance in general anaesthesia.[5,8,9] As the presynaptic regulation of neurotransmitter release is, in general, a Ca^{2+}-dependent process,[10] closing of presynaptic voltage-sensitive Ca^{2+} channels seems a logical mechanism for inhibition of transmitter release. Such a mechanism (with hyperpolarization) is used by opioid receptors.[11,12]

We have demonstrated previously that release of [^{3}H]noradrenaline from SH-SY5Y cells in response to K^+ and carbachol stimulation uses different sources of Ca^{2+}.[13] For K^+ the response is extracellular Ca^{2+} dependent whereas for carbachol the response in extracellular Ca^{2+} independent.[13] Purkiss, Nahorski and Willars have also demonstrated in this cell line that muscarinic stimulation of release used Ca^{2+} from the inositol (1,4,5) triphosphate ($Ins(1,4,5)P_3$) sensitive store[14] and muscarinic receptor stimulation is known to produce a substantial biphasic increase in $Ins(1,4,5)P_3$ mass in these cells.[15,16] While we are not claiming that the release of noradrenaline *per se* is involved in the anaesthetic state we have used the well defined characteristics of the release process to probe the site(s) of action of a range of anaesthetics, including thiopentone, propofol[17] and ketamine.[18] In this study using SH-SY5Y cells, we report that the volatile general anaesthetic agent, halothane, selectively inhibited K^+ evoked noradrenaline release suggesting that this agent inhibited Ca^{2+} entry through voltage-sensitive Ca^{2+} channels.

Materials and methods

CELL CULTURE AND BUFFERS

SH-SY5Y cells, passages 70–90, were maintained in minimum essential medium supplemented with penicillin 100 u. ml^{-1}, streptomycin 100 μg ml^{-1}, fungizone 2.5 μg ml^{-1} and 10% fetal calf serum.

R. ATCHESON, MD, FRCA, R. A. HIRST, BSC, D. J. ROWBOTHAM, MD, FRCA, D. G. LAMBERT, BSC, PHD, University Department of Anaesthesia, Leicester Royal Infirmary, Leicester LE1 5WW. K. BJORNSTROM, Department of Anaesthesia and Intensive Care, University Hospital, S-581 85 Linkoping, Sweden.
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Correspondence to D. G. L.

Stock cultures were passaged weekly and re-fed twice weekly. All experiments were performed in suspensions of cells that were harvested from confluent flasks by brief exposure to HEPES (20 mmol litre^{-1}) buffered saline (0.9%) containing EDTA (0.02%). All cells were resuspended in Krebs/HEPES buffer, pH 7.4, of the following composition (mmol litre^{-1}): Na^+ 143.3, K^+ 4.7, Ca^{2+} 2.5, Mg^{2+} 1.2, Cl^- 125.6, $H_2PO_4^{2-}$ 1.2, SO_4^{2-} 1.2, glucose 11.7 and HEPES 10. In K^+ depolarization studies, buffer Na^+ was adjusted accordingly.

[^{3}H]NORADRENALINE RELEASE

Suspensions of SH-SY5Y cells were loaded with [^{3}H]noradrenaline as described previously.[13 19] Briefly, cells were incubated with [^{3}H]noradrenaline (approximately 40 nmol litre^{-1}, 41 Ci mmol^{-1}, Amersham Bucks, UK) for 1 h at 37 °C. Loaded cells were centrifuged, resuspended in 1 ml of fresh buffer and incubated for 15 min. This procedure was repeated. Cells were then loaded into the perfusion chamber[13] and perfused at 0.5 ml min^{-1} for 15 min. For K^+ stimulation, cells were perfused with K^+ (S_1, 100 mmol litre^{-1}) for 3 min, then after 15 min were rechallenged with K^+ (S_2, 100 mmol litre^{-1}, 3 min). For muscarinic receptor stimulation experiments, the perfusion regimen was the same as that for K^+ except that cells were perfused with a single pulse of carbachol (1 mmol litre^{-1}, 3 min) in order to avoid receptor-mediated desensitization.

[^{3}H]Noradrenaline was measured in fractions (0.25 ml) of perfusate collected at 30-s intervals. Scintillation cocktail (Optipase Safe, 4 ml) was added to each fraction and the amount of [^{3}H]noradrenaline determined by scintillation spectrophotometry.

Halothane was delivered to the buffer reservoir using a pre-calibrated Fluotec agent specific vaporizer with humidified air as the carrier gas. The humidifier was positioned after the vaporizer. Vaporizer settings of 1–5 atm% were used (in random order) and air was the control. Halothane was perfused from saturated solutions for 15 min either between S_1 and S_2 (for K^+) or during the final 15-min buffer perfusion (for carbachol). Aqueous halothane concentrations were measured in both the reservoir and at the perfusion chamber outlet (see below).

MEASUREMENT OF INTRACELLULAR CALCIUM CONCENTRATION ([CA^{2+}]$_i$)

[Ca^{2+}]$_i$ was measured fluorimetrically using a Perkin-Elmer LS50B fluorimeter with excitation wavelengths set at 340 and 380 nm; emission was measured at 510 nm. SH-SY5Y cell suspensions were incubated with Fura2AM 3 µmol litre^{-1} for 30 min at 37 °C and then post-incubated with fresh buffer for another 20 min at room temperature to allow for complete ester hydrolysis.[20] Loaded cells (200 µl) were placed into a cuvette containing 1.8 ml of buffer, pre-equilibrated for 15 min with halothane (vaporizer setting 0.75, 1.5 and 3.0 atm% in random order) via "surface blowing". After another 3 min of gassing, the cells were exposed to either K^+ 80 mmol litre^{-1} or carbachol 1 mmol litre^{-1} in the continued presence of halothane or air. Excitation ratio measurements (340/380) were obtained every 1 s and converted to [Ca^{2+}]$_i$ according to Grynkiewicz, Poenie and Tsien[21] where maximum (Rmax) and minimum (Rmin) fluorescence ratios were estimated using 0.1% Triton X and EGTA 4.5 mmol litre^{-1}, respectively. Halothane did not affect the fluorescence properties of Fura2. Aqueous halothane concentrations were measured in the cuvette (see below).

MEASUREMENT OF AQUEOUS HALOTHANE CONCENTRATIONS

Buffer halothane concentrations were measured by gas chromatography according to Rutledge and colleagues.[22] After equilibration for various times at various vaporizer settings, 100 µl of buffer was injected rapidly to sealed glass vials containing

Table 1 Aqueous halothane concentrations in [^{3}H]noradrenaline release (A) and [Ca^{2+}]$_i$ (B) experiments measured at 37 °C. Data are mean (SEM) from at least five determinations. Equivalent atm% is calculated assuming 1 atm% at 37 °C and at equilibrium with the aqueous phase gives 280 µmol litre^{-1} [23]

Vaporizer setting (atm%)	Aqueous halothane (µmol litre^{-1}) Reservoir	Aqueous halothane (µmol litre^{-1}) Chamber	Equivalent (atm%) Reservoir	Equivalent (atm%) Chamber
A				
1.00	335 (24)	236 (31)	1.19 (0.08)	0.84 (0.11)
2.00	534 (54)	353 (19)	1.91 (0.19)	1.26 (0.06)
3.00	840 (50)	523 (24)	3.00 (0.18)	1.87 (0.08)
4.00	1121 (48)	645 (27)	4.00 (0.17)	2.31 (0.09)
5.00	1480 (58)	894 (21)	5.29 (0.21)	3.19 (0.08)
	Cuvette (µmol litre^{-1})		Cuvette (atm %)	
B				
0.75	245 (21)		0.88 (0.08)	
1.50	486 (35)		1.73 (0.13)	
3.00	863 (69)		3.08 (0.25)	

100 µl of heptane; 1.5 µl of the upper phase (containing halothane) was then injected onto the column. Sample integrated peak heights were compared with halothane standards made up on ice in heptane. Aqueous halothane concentrations are shown in table 1 and indicate that 15 min of "gassing" in either experimental regimen was sufficient to attain equilibrium with the aqueous phase. However, in [^{3}H]noradrenaline release experiments, halothane was lost (approximately 40%) in the perfusion system. The same perfusion chamber and pipework were therefore used throughout and the aqueous concentration taken as that at the chamber. In all subsequent data, halothane concentration refers to measured atm%.

DATA ANALYSIS

Data are presented as mean (SEM). To control for differing numbers of cells in the perfusion chamber in [^{3}H]noradrenaline experiments, release is expressed relative to the first fraction collected. Area under the normalized curves (AUC) was calculated and S_2/S_1 ratios estimated for K^+. For carbachol, the single pulse AUC was compared with control. Where appropriate data were analysed using ANOVA or Student's paired *t* test, or both.

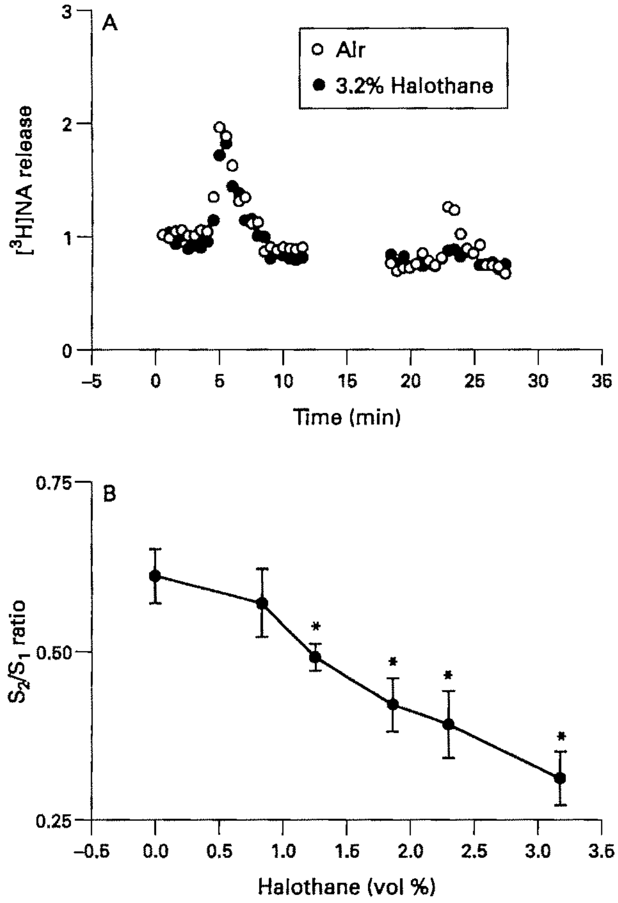

Figure 1 Halothane inhibited K^+ evoked [^{3}H]noradrenaline (NA) release from perfused SH-SY5Y human neuroblastoma cells. A: Release profile to two 3-min pulses (S_1 and S_2) of K^+ 100 mmol litre^{-1} (single experiment from n=5). To control for varying numbers of cells in the chambers, data are expressed relative to the first fraction collected. The area under the normalized curves were estimated and S_2/S_1 ratios calculated. Dose-dependent reduction in S_2/S_1 ratio is presented in (B) from mean (SEM) of n=5–7. Whole curve $P<0.05$ by ANOVA and *$P<0.05$ compared with 0% halothane (air).

Table 2 Effects of halothane on carbachol evoked [^{3}H]noradrenaline release (A) and increase in $[Ca^{2+}]_i$ (B). All data are mean (SEM). No significant differences between groups

Halothane (atm%)	*n*	[^{3}H]noradrenaline release (%air)	
A			
Air	5	100.0	
0.84	5	93.5 (3.2)	
1.87	5	110.4 (3.2)	
3.19	5	87.0 (2.1)	
		$[Ca^{2+}]_i$ (nmol litre^{-1}-basal)	
		Peak	Plateau
B			
Air	5	449 (57)	109 (16)
0.88	5	435 (89)	109 (23)
1.73	5	475 (45)	131 (9)
3.08	5	321 (69)	74 (14)

Results

Both K^+ 100 mmol litre^{-1} (fig. 1A) and carbachol 1 mmol litre^{-1} (data not shown) produced a monophasic increase in the release of [^{3}H]noradrenaline from undifferentiated SH-SY5Y human neuroblastoma cells. For K^+ a second monophasic release profile could be elicited 15 min after the first challenge with K^+, yielding an S_2/S_1 ratio of 0.61 (0.04) (n=7). When applied between S_1 and S_2, halothane produced dose-dependent inhibition of S_2 (fig. 1A) and hence S_2/S_1 ratio (fig. 1B). As maximum inhibition was not achieved, we could not estimate an IC_{50} value but significant ($P<0.05$) inhibition (17%) occurred at 1.26 atm% (approximately 1.5 MAC). Halothane did not affect basal (data not shown, n=2) or carbachol evoked [^{3}H]noradrenaline release (table 2).

Both K^+ 80 mmol litre^{-1} (fig. 2A) and carbachol 1 mmol litre^{-1} (data not shown) produced a biphasic increase in $[Ca^{2+}]_i$. For K^+ the peak value was 196 (11) nmol litre^{-1} and the plateau level (2 min after stimulus) was 122 (14) nmol litre^{-1}. Corresponding values for carbachol were 543 (56) nmol litre^{-1} and 204 (12) nmol litre^{-1}, respectively. After a 15-min equilibration period, halothane produced a dose-dependent inhibition of the K^+ peak increase in $[Ca^{2+}]_i$ (fig. 2). As maximum inhibition was not achieved, we could not estimate an IC_{50} value but significant inhibition (29%) occurred at 0.88 atm% (approximately 1.2 MAC). Basal, plateau (fig. 2) and carbachol (table 2) evoked increases in $[Ca^{2+}]_i$ were unaffected by halothane.

Discussion

We have demonstrated that the volatile general anaesthetic halothane produced a dose-dependent

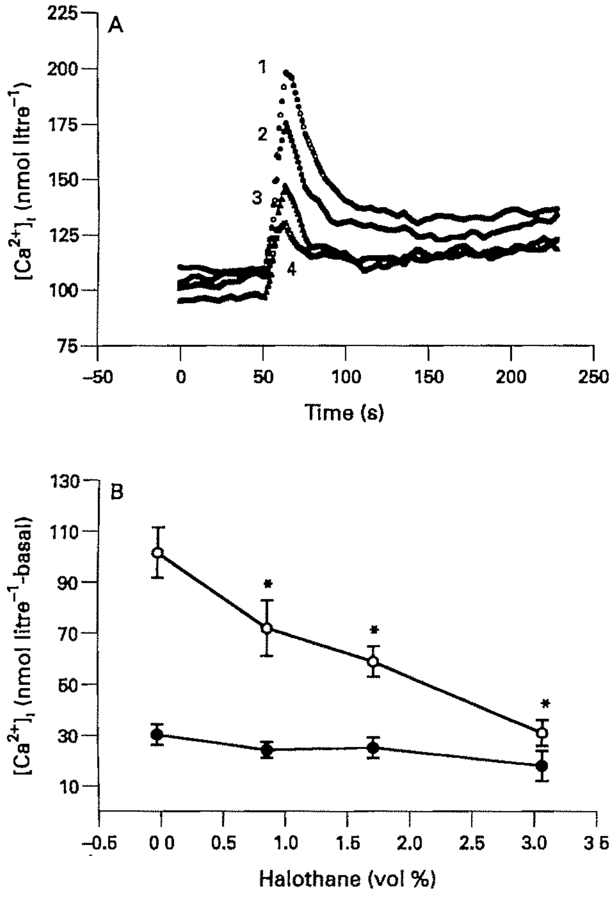

Figure 2 Halothane reduced peak but not plateau phase increase in $[Ca^{2+}]_i$ in Fura2 loaded SH-SY5Y human neuroblastoma cells after stimulation with K^+ 80 mmol litre^{-1}. A: Time course to K^+ 80 mmol litre^{-1} challenge for air control (1), 0.88% (2), 1.73% (3) and 3.08% (4) halothane, data from a single representative experiment. Basal levels of $[Ca^{2+}]_i$ (air 94 (6) nmol litre^{-1}, *n*=13; 0.88 atm% 106 (9) nmol litre^{-1}, *n*=11; 1.73 atm% 98 (5) nmol litre^{-1}, *n*=12; 3.00 atm% 100 (5) nmol litre^{-1}, *n*=12) were unaffected by halothane. The dose–response curve for peak (○) and plateau (●) phase is shown in (B), after subtraction of a variable basal. Data are mean (SEM) from *n*=6–8. The peak phase curve was $P<0.05$ by ANOVA and all concentrations were reduced significantly ($^*P<0.05$) compared with 0% halothane (air).

inhibition of K^+ but not carbachol evoked [^{3}H]noradrenaline release from SH-SY5Y human neuroblastoma cells. As K^+ (but not carbachol) evoked release is extracellular Ca^{2+} dependent[13] these data suggest that halothane inhibited Ca^{2+} entry through voltage-sensitive Ca^{2+} channels. Indeed, further studies in Fura2 loaded SH-SY5Y cells showed dose-dependent inhibition of K^+ but not carbachol evoked increase in intracellular Ca^{2+}. This indicates that halothane reduced voltage-sensitive calcium channel (VSCC) gated Ca^{2+} influx in these cells resulting in reduced [^{3}H]noradrenaline release. Moreover, the concentrations required to achieve significant inhibition (1.26 atm% and 0.88 atm% for [^{3}H]noradrenaline release and increased intracellular Ca^{2+}, respectively) agree well with clinically relevant concentrations for this agent.[23] A clinical estimate of IC_{50} is the minimum alveolar concentration (MAC) of agent that inhibits movement to skin incision in 50% of patients; for halothane this is 0.75 atm%.[23] However, while this value agrees well with our data for significant inhibition, extrapolation of MAC (for a whole organism) to measurements made with isolated neuronal cells is difficult, and should be undertaken carefully.

In SH-SY5Y cells, depolarization with high doses of K^+ produces an increase in Ca^{2+} influx through both L- and N-type voltage-sensitive Ca^{2+} channels measured in Fura2 loaded cells.[24] In addition, the existence of these channels has been demonstrated electrophysiologically, although L channels are likely to be expressed at low levels.[25] Indeed, we have noted that SH-SY5Y cells express low levels of L-type VSCC (<10 fmol/mg protein [^{3}H]PN200-110 binding sites[26]). This study gives no indication of which channel (L, N or both) is inhibited by halothane. For carbachol, the increase in intracellular Ca^{2+} was biphasic with the peak phase representing release of Ca^{2+} from an $Ins(1,4,5)P_3$ sensitive store and the plateau phase representing Ca^{2+} influx through a receptor operated Ca^{2+} channel.[27 28] The time course for generation of $Ins(1,4,5)P_3$ was also biphasic showing a close temporal (and dose) relationship.[15 16] Our data clearly showed that muscarinic agonist increased intracellular [Ca^{2+}] and the subsequent increased [^{3}H]noradrenaline release was relatively unaffected by halothane.

Volatile anaesthetics have been shown to inhibit the release of a variety of neurotransmitters from various tissues.[2] Halothane inhibits the release of catecholamines from bovine adrenal chromaffin cells at clinically relevant concentrations in response to carbachol (presumably acting at nicotinic receptors in this preparation) but not depolarization.[29 30] Similar findings have also been reported for enflurane, isoflurane and methoxyflurane.[30] In our study we found the opposite effect, with K^+ but not carbachol evoked release being reduced. This may result from muscarinic M_3 receptors coupling to release in SH-SY5Y cells and nicotinic receptors coupling to release in chromaffin cells. However, it should also be noted that some batches of SH-SY5Y cells express nicotinic receptors and nicotine has been shown to increase intracellular Ca^{2+} and stimulate [^{3}H]noradrenaline release.[31 32] However, in our hands nicotinic receptor stimulation did not produce significant depolarization or Ca^{2+} entry.[33] Bazil and Minneman[34] and Mantz and colleagues[35] reported in rat cerebrocortical slices and rat striatal synaptosomes that halothane reduced depolarization evoked catecholamine release at clinically relevant concentrations. Interestingly, in the former study [^{3}H]acetylcholine release was unaffected.[34] Halothane and isoflurane inhibited K^+ evoked catecholamine secretion and increase in intracellular Ca^{2+} through L-type VSCC from PC12 cells at clinically relevant concentrations.[36] In addition to these reported inhibitory effects of volatile anaesthetics, stimulatory effects have also been reported; for example, halothane, enflurane, isoflurane and methoxyflurane enhanced phorbol ester evoked catecholamine release from PC12 cells.[37]

Volatile anaesthetic agents have been shown to affect intracellular Ca^{2+} in many cell types.[9 36] Both inhibitory and stimulatory effects have been observed, with volatile agents inhibiting Ca^{2+} entry through a variety of channels,[29 38 39] promoting release from intracellular (caffeine, ryanodine and $Ins(1,4,5)P_3$ sensitive) Ca^{2+} stores[41 42 44] and inhibiting release of Ca^{2+} from intracellular stores.[43 44] However, while there are many studies of the effects of volatile agents on Ca^{2+} homeostasis, the role of this divalent cation in the mechanisms of general anaesthesia still remains controversial, especially with respect to VSCC activity.[5 8 9] In addition, the potency of halothane for the production of anaesthesia in humans displays a steep curve, with MAC=0.75 atm%,[5] whereas inhibition of VSCC in this study showed a more shallow curve. We feel that the comparison of dose-related effects of halothane on VSCC activity with estimation of MAC in a population of subjects should be made with caution. While inhibition of Ca^{2+} entry in K^+ depolarized SH-SY5Y cells reported here (and subsequent inhibition of $[^3H]$noradrenaline release) is in general agreement with the studies noted above, the insensitivity of carbachol stimulated increase in intracellular Ca^{2+} is worthy of special note. Others have reported that agonist (non-depolarizing) stimulated increases in intracellular Ca^{2+} can be reduced by volatile general anaesthetics, for example in GH_3 pituitary cells, receptor operated Ca^{2+} channel activity is blocked by halothane.[45] There are few reports of the effects of volatile anaesthetic agents on phosphoinositide hydrolysis.[46 47] We have measured $Ins(1,4,5)P_3$ mass formation in response to halothane and isoflurane in SH-SY5Y cells and reported dose-dependent (EC_{50} for halothane at 0.75 atm%) enhancement of carbachol stimulated $Ins(1,4,5)P_3$ formation.[47] In addition, basal $Ins(1,4,5)P_3$ formation was also enhanced. These data are at variance with the lack of effect of halothane on basal or carbachol stimulated increase in intracellular Ca^{2+} and $[^3H]$noradrenaline release. However, the increase in $Ins(1,4,5)P_3$ formation was relatively small in comparison with the increase produced by carbachol.

In summary, we have shown that halothane, at concentrations which produce general anaesthesia, inhibited depolarization (but not muscarinic agonist) evoked release of $[^3H]$noradrenaline by reducing Ca^{2+} influx through VSCC. These data are in general agreement with our previous findings for propofol, thiopentone[17] and ketamine[18] and adds weight to our hypothesis that VSCC may be a target site for anaesthetic agents. Clearly, this hypothesis will need further rigorous testing.

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Role of endothelium in the modulation of isoflurane-induced vasodilatation in rat thoracic aorta

P. KIRSTETTER, F. LAGNEAU, O. LUCAS, Y. KRUPA AND J. MARTY

Summary

The mechanisms by which endothelium attenuates vasodilatation caused by isoflurane are not well understood. We examined the role of endothelium-derived substances, nitric oxide (NO), endothelium-derived hyperpolarizing factors (EDHF), prostanoids and endothelins in the response to isoflurane in rat thoracic aorta. Increasing cumulative concentrations of isoflurane were administered to aortic rings suspended in Hepes solution and preconstricted with either phenylephrine 10^{-6} mol litre^{-1} or KCl 40 mmol litre^{-1} (which inhibit EDHF). Rings were intact, denuded or incubated with an inhibitor of nitric oxide synthesis (Nω-nitro-L-arginine (LNNA 5×10^{-5} mol litre^{-1}), an inhibitor of prostanoid synthesis (indomethacin 10^{-5} mol litre^{-1}) or a blocker of the vascular receptors to endothelins (cyclo (-D-trp-D-Asp-Pro-D-Val-Leu (BQ 123 10^{-5} mol litre^{-1})). Endothelium attenuated isoflurane-induced vasodilatation in KCl-constricted rings at concentrations of 4% (mean 95 (SEM 4) % *vs* 72 (4) %; $P=0.0005$) and 5% (100 (4) % *vs* 80 (4) %; $P=0.0008$) and in phenylephrine constricted rings at concentrations of 4% (54 (8) % *vs* 35 (3) %; $P=0.04$) and 5% (78 (10) % *vs* 49 (5) %; $P=0.03$). Relaxation was significantly greater in rings treated with LNNA than in intact rings at concentrations of 4% (85 (4) % *vs* 72 (4) %; $P=0.0005$) and 5% (90 (4) % *vs* 80 (4) %; $P=0.0008$). Indomethacin and BQ 123 did not alter isoflurane-induced vasodilatation. We conclude that endothelium attenuated the vasodilator effect of isoflurane by a mechanism which was abolished by inhibition of nitric oxide. We hypothesize that isoflurane inhibits the release of nitric oxide, leading to a relative vasoconstriction counterbalancing its vasodilator effect. In contrast, EDHF, prostanoids and endothelins were not involved in the attenuation of isoflurane-induced vasodilatation. (*Br. J. Anaesth.* 1997; **79**: 84–87).

Key words
Anaesthetics volatile, isoflurane. Muscle vascular, responses. Pharmacology, nitric oxide. Rat.

Isoflurane is a volatile anaesthetic which relaxes vascular smooth muscle cells.[1–7] It has been shown previously that vessels without endothelium relaxed more than vessels with endothelium,[4,7] suggesting that isoflurane may either decrease the release of endothelium-derived relaxing factors or increase the release of endothelium-derived contracting factors. A previous study examined the role of nitric oxide (an endothelium-derived relaxing factor) and found that relaxation was comparable between denuded vessels and vessels treated with an inhibitor of nitric oxide synthase.[7] It has also been shown that the release of nitric oxide was decreased by volatile anaesthetics[8–15] suggesting that nitric oxide accounts for the lesser degree of relaxation obtained in intact vessels compared with denuded vessels.

Even if nitric oxide is responsible for this effect, isoflurane may also inhibit the release of other endothelium-derived vasodilators (i.e. prostacyclin and endothelium-derived hyperpolarizing factors (EDHF)) or may increase the release of endothelium-derived vasoconstrictors (i.e. endothelins and thromboxane A_2). It has been shown recently that prostanoids and EDHF were decreased by isoflurane,[16,17] but their role in modulating the action of volatile anaesthetics on the intact vessel has not been investigated. In addition, interactions between isoflurane and release of endothelins by vessels have not been examined.

The aim of this study was to examine the role of nitric oxide, prostanoids, EDHF and endothelins in the modulation of relaxation induced by isoflurane in isolated rat thoracic aorta.

Materials and methods

ANIMALS

We used male Sprague–Dawley rats (300–350 g) (Iffa-Credo, France). The study was approved by the French Agriculture Office in conformity with European Legislation Involving Animals.

P. KIRSTETTER*, MD, F. LAGNEAU, MD, O. LUCAS, MD, Y. KRUPA, MD, J MARTY, MD, Department of Anaesthesia, Hôpital Beaujon, Clichy and INSERM U-408, Hôpital Bichat, Paris, France.
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*Present address for correspondence: Department of Anaesthesia, Hôpital Beaujon, 100 bd du Gal-Leclerc, 92118 Clichy cedex, France.

PREPARATION OF AORTIC RINGS

Animals were anaesthetized with pentobarbitone 50 mg kg^{-1} i.p., which does not alter the reactivity of vessels removed from these animals.[18] The thoracic aorta was removed and placed in modified Hepes buffer (37 °C) aerated with a mixture of 95% oxygen and 5% carbon dioxide. Aorta were dissected clean of fat and extraneous tissues and divided into 3.5–4.0-mm ring segments. In some rings, endothelium was removed mechanically by gently rubbing the intimal surface with a stainless steel rod. The rings were suspended between two L-shaped stainless steel hooks and placed in a 10-ml, water-jacketed organ chamber containing a solution composed of (mmol $litre^{-1}$) NaCl 118.2, KCl 4.7, $NaHCO_3$ 25.0, KH_2PO_4 1.2, $MgSO_4$ 1.2, $CaCl_2$ 2.5, glucose 11.1 and Hepes 5. Organ chambers were aerated continuously with 95% oxygen and 5% carbon dioxide with pH maintained at 7.35–7.40.[19] Temperature was maintained constant at 37 °C. Isometric tensions were measured (g) using a force displacement transducer (UF1 Pioden Controls, Paris, France) connected to the upper hook. Tensions were recorded on a Servo trace recorder (Sefram, Paris). During the equilibration period of 60 min, the buffer was changed every 15 min and resting tension was adjusted periodically to 1.5 g. Active contraction was induced with KCl 40 mmol $litre^{-1}$ and the integrity of endothelium was assessed by testing the relaxation produced by the addition of acetylcholine 10^{-6} mol $litre^{-1}$.[20] Endothelium was considered intact when acetylcholine elicited a minimum of 30% vasodilatation. Endothelium was considered removed when acetylcholine induced no vasodilatation. After acetylcholine testing, the rings were washed and re-equilibrated to baseline tension for 60 min. After this new period of stability, rings were constricted with KCl 40 mmol $litre^{-1}$ or phenylephrine 10^{-6} mol $litre^{-1}$. Isoflurane was then delivered using a calibrated agent-specific vaporizer (Abbott, France). The concentrations of isoflurane in the gas phase were monitored and adjusted using an anaesthetic agent monitor. Aortic rings were exposed to cumulative concentrations of isoflurane of 1–5%. Each concentrations was maintained until the effect on the aortic ring reached a plateau (i.e. an average of 10 min). The vasodilator effect of isoflurane was expressed as percentage decrease in tension compared with the plateau reached after KCl or phenylephrine.

ROLE OF ENDOTHELIUM AND ENDOTHELIUM-DERIVED NITRIC OXIDE, PROSTANOIDS, EDHF AND ENDOTHELINS IN ISOFLURANE-INDUCED VASODILATATION

The role of endothelium was assessed by comparing isoflurane-induced vasodilatation between intact and denuded rings. To assess the role of EDHF in the relaxation of intact and denuded rings, the experiment was conducted in phenylephrine preconstricted rings (intact rings $n=12$, denuded rings $n=12$), and in KCl (which inhibits EDHF)[21] preconstricted rings (intact rings $n=12$, denuded rings $n=12$).

The role of nitric oxide was assessed in KCl-preconstricted vessels by comparing isoflurane-induced vasodilatation between intact rings ($n=12$) and rings incubated with an inhibitor of endothelial nitric oxide synthase, Nω-nitro-L-arginine (LNNA) 5×10^{-5} mol $litre^{-1}$ ($n=12$).

The role of prostanoids was assessed in KCl-preconstricted vessels by comparing isoflurane-induced vasodilatation between intact rings ($n=12$) and rings incubated with an inhibitor of cyclo-oxygenase, indomethacin 10^{-5} mol $litre^{-1}$ ($n=12$).

The role of endothelins was assessed in KCl-preconstricted vessels by comparing isoflurane-induced vasodilatation between intact rings ($n=12$) and rings incubated with an inhibitor of smooth muscle cell receptors to endothelins (ET-A receptors), cyclo (-D-trp-D-Asp-Pro-D-Val-Leu) (BQ 123) 10^{-5} mol $litre^{-1}$ ($n=12$).[22 23]

Drugs used in this study were phenylephrine, acetylcholine, LNNA and indomethacin (Sigma Chemical, France), BQ 123 (Neosystem, France) and isoflurane (Abbott, France).

STATISTICAL ANALYSIS

Data are expressed as percentage decrease in tension compared with tensions developed after KCl 40 mmol $litre^{-1}$. Data are expressed as mean (SEM). Data were analysed using ANOVA. Differences were considered significant if $P<0.05$.

Results

Isoflurane produced dose-dependent relaxation in all groups of rings.

In KCl-preconstricted vessels, isoflurane-induced relaxation was significantly greater in denuded than

Table 1 Vasodilatation induced after administration of increasing concentrations of isoflurane (Iso) (1–5%) in rings of rat thoracic aorta (mean (SEM)). Baseline=Absolute tension developed after KCL 40 mol $litre^{-1}$; Endo.=intact rings; Denuded=rings without endothelium; LNNA=rings treated with Nω-nitro-L-arginine, an inhibitor of nitric oxide synthase; Indo.=rings treated with indomethacin, an inhibitor of prostanoid synthesis; BQ 123=rings treated with -D-trp-D-Asp-Pro-D-Val-Leu, an antagonist of vascular receptors to endothelins. *$P<0.05$ compared with basal values

	Absolute tension (g)						Decrease in tension (% of control)				
Groups	Basal	Iso 1%	Iso 2%	Iso 3%	Iso 4%	Iso 5%	Iso 1%	Iso 2%	Iso 3%	Iso 4%	Iso 5%
Endo. ($n=12$)	1.5 (0.1)	1.3 (0.3)	0.9 (0.1)	0.5 (0.1)	0.4 (0.1)	0.3 (0.1)	13 (3)	41 (5)	62 (5)	72 (4)	80 (4)
Denuded ($n=12$)	2.4 (0.2)*	2.2 (0.5)*	1.3 (0.2)	0.6 (0.2)	0 2 (0.1)	0.1 (0.1)	8 (2)	45 (7)	76 (7)*	95 (4)*	100 (4)*
LNNA ($n=12$)	3.1 (0.3)*	2.9 (0.2)*	1.7 (0.3)*	0.8 (0.2)	0.5 (0.2)	0.3 (0.1)	6 (1)	49 (8)*	74 (8)	85 (4)*	90 (3)*
Indo. ($n=10$)	2.2 (0 2)*	3.0 (0.4)*	1.2 (0.2)	0.7 (0.2)	0.5 (0.2)	0.3 (0.1)	12 (3)	50 (6)	68 (6)	77 (4)	85 (3)
BQ 123 ($n=12$)	2.9 (0.2)*	2.7 (0.3)*	1.8 (0.1)*	1.0 (0.1)*	0.7 (0.1)*	0.5(0.1)	4 (2)	36 (4)*	59 (4)	73 (2)	81 (2)

Table 2 Vasoldilatation induced after administration of increasing concentrations of isoflurane (Iso) (1–5%) in rings of rat thoracic aorta. Baseline=Absolute tension developed after phenylephrine 10^{-6} mol litre^{-1}. Endo.=intact rings; Denuded=rings without endothelium. *$P<0.05$ compared with basal values

	Absolute tension (g)						Decrease in tension (% of control)				
Groups	Basal	Iso 1%	Iso 2%	Iso3 %	Iso 4%	Iso 5%	Iso 1%	Iso2 %	Iso 3%	Iso4 %	Iso 5%
Endo. (n=12)	2.6 (0.3)	2.6 (0.3)	2.4 (0.3)	2.1 (0.2)	1.7 (0.2)	1.4 (0.2)	2 (1)	6 (1)	20 (2)	35 (3)	49 (5)
Denuded (n=12)	1.5 (0.3)*	1.5 (0.3)*	1.4 (0.3)*	1.2 (0.3)*	0.9 (0.3)*	0.7 (0.3)*	2 (1)	11 (2)*	30 (4)*	54 (8)*	78 (10)*

in intact rings at concentrations of 4% and 5% (table 1). In phenylephrine-constricted vessels, isoflurane-induced relaxation was significantly greater in denuded than in intact rings at concentrations of 4% and 5% (table 2). The difference in vasodilatation between intact and denuded rings was comparable between vessels constricted with phenylephrine and vessels constricted with KCl at 4% isoflurane (23 (4) % *vs* 19 (2) %; ns) and at 5% isoflurane (20 (3) % *vs* 29 (3) %; ns).

Isoflurane-induced relaxation was significantly greater in rings treated with LNNA than in intact rings at concentrations of 4% and 5% and was comparable with relaxation obtained in denuded rings (table 1).

Relaxations were not significantly different between intact rings and rings treated with BQ 123 or indomethacin (table 1).

Discussion

We have shown that isoflurane dose dependently relaxed aortic rings via an endothelium-independent mechanism[1–7] as vasodilatation obtained in intact vessels was present in vessels without endothelium. However, we found that the presence of endothelium modified the response to isoflurane, as denuded vessels were relaxed more than intact vessels.

The fact that vasodilatation was greater in denuded than in intact vessels suggests that isoflurane may have altered endothelial control of vascular tone. To explain such an effect, we hypothesized that isoflurane may either decrease release of endothelium-derived relaxing factors or increase release of endothelium-derived contracting factors[4 7]: of the endothelium-derived relaxing substances, we examined nitric oxide, EDHF and prostacyclin; of the endothelium-derived constricting factors, we examined endothelins and thromboxane A_2.

Nitric oxide is a labile molecule synthesized by endothelium which relaxes vessels by increasing the concentration of 3' 5'-guanosine monophosphate (cGMP) within the vasculature[24] and by hyperpolarizing smooth muscle cells.[25] To assess the role of nitric oxide, we have compared the effect of isoflurane between intact rings and rings incubated with LNNA. We found that vessels treated with LNNA relaxed more than intact rings. This indicates that nitric oxide did not mediate isoflurane-induced vasodilatation but rather modulated this effect. Indeed, if nitric oxide has a role in isoflurane-induced vasodilatation, vessels treated with LNNA should dilate less than intact vessels, and not the contrary. Therefore, we suggest that the fact that relaxation was less in intact compared with LNNA-treated vessels was possibly a result of inhibition of release of nitric oxide by isoflurane. This hypothesis is supported by the study of Brendel and Johns,[7] who showed similar results in the aorta, and by studies which demonstrated that volatile anaesthetics decreased the amount of nitric oxide produced by endothelial cells. The mechanisms involved in this attenuation produced by nitric oxide do not involve smooth muscle cell hyperpolarization as similar results were obtained in the presence of KCl, which inhibits hyperpolarization.[25] Isoflurane-induced decrease in production or stability of nitric oxide[15] may lead to a relative vasoconstriction counterbalancing the relaxation produced by isoflurane.

The effects of endothelium-derived hyperpolarizing factors (EDHF) are not well understood but a vasodilator action has been documented.[26] To assess the role of EDHF in the difference in relaxation between intact and denuded rings, experiments were conducted in vessels constricted with phenylephrine and KCl, which are known to inhibit the action of EDHF.[21] We found that the difference in relaxation between intact and denuded rings persisted in the absence of EDHF. Therefore, we conclude that EDHF did not play a role in modulating isoflurane-induced vasodilatation.

Prostanoids are end products of arachidonic acid metabolism and are synthesized by endothelium via activation of cyclo-oxygenase.[27] Prostacyclin is a vasodilator while thromboxane A_2 is a vasoconstrictor.[27] To assess the role of prostanoids in the difference in relaxation between intact and denuded rings, the effect of isoflurane was compared between intact rings and rings incubated with indomethacin. We found that relaxation in rings treated with indomethacin was comparable with that of intact vessels. Therefore, modulation of isoflurane-induced vasodilatation was not mediated by release of a contracting prostanoid or by inhibition of the release of a relaxing factor.

Endothelins are peptides synthesized by endothelium that act on adjacent smooth muscle cells to produce vasoconstriction.[22] This effect is mediated via activation of specific receptors (ET-A receptors).[22 23] As the difference in relaxation between intact and denuded rings may result from increased production of endothelins, we compared the effect of isoflurane on intact rings and rings incubated with BQ 123, a specific antagonist of ET-A receptors.[23] We found that relaxation of rings treated with BQ 123 was comparable with that in intact rings. Therefore, endothelins do not play a role in modulating isoflurane-induced vasodilatation.

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Halothane reduces reperfusion injury after regional ischaemia in the rabbit heart *in vivo*

W. SCHLACK, B. PRECKEL, H. BARTHEL, D. OBAL AND V. THÄMER

Summary

In addition to having anti-ischaemic effects, halothane can protect isolated rat hearts and isolated cardiomyocytes against reperfusion injury of the "oxygen paradox" type. The aim of this study was to investigate if halothane can also protect against myocardial reperfusion injury *in vivo.* Twenty-two rabbits anaesthetized with α-chloralose underwent 30 min of occlusion of a major coronary artery and 2 h of subsequent reperfusion. Seven animals received 1 MAC of halothane for the first 15 min of reperfusion (halothane group), and eight animals served as untreated controls (control group). In seven additional animals, the haemodynamic effects of halothane were antagonized by an i.v. infusion of noradrenaline (halothane–noradrenaline group). We measured cardiac output (CO) by an ultrasonic flow probe around the ascending aorta, left ventricular pressure (LVP) by a tip manometer and infarct size by triphenyltetrazolium staining. Baseline LVP was mean 92 (SEM 4) mm Hg and CO was 289 (16) ml min^{-1}. During coronary occlusion, LVP was reduced to 86 (4) % of baseline and CO to 84 (4)% (similar in all groups). During halothane administration at reperfusion, LVP declined further to 55 (6) % of baseline and CO to 66 (9) % ($P<0.05$ halothane group *vs* control group). Noradrenaline prevented the reduction in LVP (halothane–noradrenaline group 87 (5) % of baseline, control group 84 (6) %) and reduction in CO (halothane–noradrenaline group 89 (5) %, control group 83 (6) %). Infarct size was 49 (6) % of the area at risk in controls and was reduced markedly by administration of halothane to 32 (3) % in the halothane group ($P<0.05$) and to 30 (3) % in the halothane–noradrenaline group ($P<0.05$). Treatment with halothane during the early reperfusion period after myocardial ischaemia protected the myocardium against infarction *in vivo,* independent of the haemodynamic effects of halothane. (*Br. J. Anaesth.* 1997; **79**: 88–96).

Key words
Anaesthetics volatile, halothane. Heart, ischaemia. Heart, reperfusion injury. Heart, myocardial function. Model, rabbit. Rabbit.

The anti-ischaemic effects of halothane were reported as early as 1969 by Spieckermann and colleagues[1] for dog hearts during normothermic ischaemia, and a protective effect of halothane against ischaemic injury was confirmed in several experimental studies.[2–7] Recently, we have shown in isolated rat hearts that cardiac protection by halothane was more pronounced if it was administered after ischaemia during reperfusion than if it was given during the ischaemic period itself,[8] providing some evidence for a protective effect of halothane against the mechanisms of reperfusion injury. Using isolated anoxic reoxygenated cardiomyocytes, it was possible to confirm a protective effect against lethal reperfusion injury of the "oxygen paradox" type and to identify a protective mechanism of halothane against this type of reperfusion injury.[9 10] Halothane 1.5 MAC, given during reoxygenation, prevented reoxygenation-induced Ca^{2+} oscillations at the Ca^{2+}-dependent–Ca^{2+}-release channel of the sarcoplasmic reticulum. These Ca^{2+} oscillations are responsible for cellular hypercontracture and cell death at early reperfusion.[11]

However, a specific protective action of halothane against reperfusion injury is evident only from *in vitro* studies that investigated reperfusion injury of the oxygen paradox type. *In vivo,* the pathophysiology of reperfusion injury is more complex. It is possible that several mechanisms of lethal reperfusion injury may exist, the oxygen paradox being but one; other mechanisms may involve free radicals, activated leucocytes and recurrent ischaemia by vascular obstruction.[12]

In this study, the protective effect of halothane against lethal reperfusion injury was investigated in an *in vivo* animal model with coronary artery occlusion and subsequent reperfusion. Previous *in vivo* studies have found a reduction in myocardial injury under ischaemia–reperfusion conditions in the presence of halothane.[2 13] However, from these studies, it was not possible to distinguish between anti-ischaemic effects and effects against reperfusion injury, because halothane was given before the onset

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WOLFGANG SCHLACK*, MD, DEAA, BENEDIKT PRECKEL, MD, HOLGER BARTHEL, CAND MD, DETLEF OBAL, CAND MD, VOLKER THÄMER, MD, Institut für Klinische Anaesthesiologie and Physiologisches Institut I, Heinrich-Heine-Universität Düsseldorf, Düsseldorf, Germany. Accepted for publication: March 10, 1997.

*Address for correspondence: Institut für Klinische Anaesthesiologie, Heinrich-Heine-Universität Düsseldorf, Postfach 10 10 07, D-40001 Düsseldorf, Germany.

of ischaemia and during ischaemia. It is known that other negative inotropic drugs (e.g. calcium antagonists[14 15] or beta blockers[16 17]) have potent anti-ischaemic effects when given before or during ischaemia. In this study, we administered halothane only during the initial reperfusion period (15 min). Halothane is known to reduce sympathoadrenergic activity, myocardial inotropy and ventricular loading. To investigate if these haemodynamic effects may be responsible for a myocardial protective effect of halothane *in vivo*, arterial pressure was kept stable in one experimental group by continuous infusion of noradrenaline during administration of halothane.

Materials and methods

The study was performed in accordance with the regulations of the German Animal Protection Law and after obtaining permission from the Animal Care Committee of the District of Düsseldorf.

ANIMAL PREPARATION

After local anaesthesia with EMLA cream, a marginal ear vein was cannulated in 29 New Zealand White rabbits of both sexes, weighing 2.2–4.2 (mean 3.8) kg. The animals were anaesthetized with sodium thiopentone 15–30 mg kg^{-1} i.v. followed by α-chloralose 80 mg kg^{-1} i.v. The trachea was intubated with a Woodbridge tube (3.5 mm id) and ventilation was controlled using a Starling pump (Type 874/052, Braun Melsungen, Germany). Ventilatory frequency was set at 30–35 bpm and tidal volume at 15–20 ml in order to maintain end-expiratory P_{CO_2} at approximately 4.4 kPa (Datex Capnomac Ultima, Division of Instrumentarium Corp., Helsinki, Finland). Arterial blood-gas tensions, haemoglobin concentration and packed cell volume were assessed at regular intervals (before surgery, before the study and at the end of the study). Surface electrocardiogram (ECG, Siemens-Elema AB, Medicins and Technik, Selna, Sweden) was recorded continuously. Anaesthesia was maintained by continuous infusion of α-chloralose 40 mg kg^{-1} h^{-1}. Additional bolus doses were given as needed during surgery. Adequacy of this anaesthesia regimen was demonstrated by lack of muscle movement and haemodynamic responses during surgery.

For measurement of aortic pressure (AOP), a 20-gauge Teflon catheter was advanced from the left carotid artery into the aortic arch and connected to a Statham transducer (PD23, Gould, Cleveland, OH, USA). After cannulation of the external jugular vein, animals received a continuous infusion of normal saline 15 ml kg^{-1} h^{-1} to compensate for fluid losses. Neuromuscular block during thoracotomy was produced with a single dose of pancuronium 0.1 mg kg^{-1} i.v. Body temperature was measured with a rectal thermometer and kept within physiological limits by a heating pad and an infrared lamp.

After median sternotomy and pericardiotomy, an ultrasonic flow probe was placed around the ascending aorta in order to measure left ventricular stroke volume minus coronary flow volume (4S or 6S ultrasonic flow probe, T 208, Transonic Systems Inc., Ithaca, NY, USA). Left ventricular (LV) pressure was monitored using a catheter tip manometer (Micro-Tip Pressure Transducer, Sensodyn S PO SF-1, Braun Melsungen AG, Melsungen, Germany) introduced via the left atrium. A ligature snare was passed around a major coronary artery for later occlusion. After completion of the preparation, the thoracotomy was covered with plastic film to lessen evaporative and convective heat loss. Temperature was measured inside the pericardial cradle (GTH 1160, Digital Thermometer, Geisinger Electronic, Germany) and maintained at 38.5±0.3 °C by adjusting the heating pad and the infrared lamp. Figure 1 illustrates the preparation of the heart.

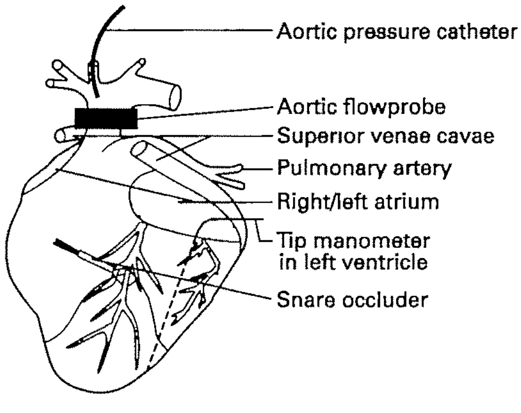

Figure 1 Experimental preparation

EXPERIMENTAL PROGRAMME

Fifteen minutes after surgery had been completed, baseline measurements were performed. In two rabbits, halothane was given in concentrations of 0.5, 0.75, 1.0 and 1.5 MAC in order to assess the haemodynamic effects of halothane on normal myocardium in this experimental preparation during α-chloralose anaesthesia. For the ischaemia–reperfusion experiments, after baseline measurements the prepared coronary artery was occluded by tightening the snare. The effectiveness of this manoeuvre was verified by the appearance of epicardial cyanosis and ECG changes. Ventricular fibrillation during coronary occlusion was treated by electrical defibrillation (5 J, DCS261 Defibrillator, Piekser, Ratingen, Germany). After 30 min of occlusion, the snare occluder was released. Reperfusion was verified by the disappearance of epicardial cyanosis.

After 120 min of reperfusion, the heart was arrested by injection of 20 ml of potassium chloride solution 16 mmol $litre^{-1}$ into the left atrium, quickly excised and mounted on a modified Langendorff apparatus for perfusion with ice-cold normal saline via the aortic root at a perfusion pressure of 40 cm H_2O in order to wash out intravascular blood. After 5 min of perfusion, the coronary artery was re-occluded and the remainder of the myocardium was perfused through the aortic root with 0.2% Evans blue in normal saline for 10 min. Intravascular Evans blue was then washed out by perfusion with normal saline for 5 min. This treatment identifies the area at risk as unstained. The heart was then cut into transverse slices, 2 mm thick. The weight of each slice was measured and the slices were stained in buffered 0.75% triphenyltetrazolium chloride solution at 38 °C to identify viable and necrotic tissue within the area at risk.[18] The area at risk, and the infarcted area, were determined by planimetry. In the rabbit, the volume of the area at risk has to exceed a certain limit before infarction develops.[19] Therefore, animals with an area at risk of less than 0.5 g were excluded from analysis.

Eight rabbits underwent the ischaemia–reperfusion programme without further intervention (control group). In seven rabbits, halothane was added to the inspired gas (Vapor 19.3, Drägerwerke AG, Lübeck, Germany) starting 3 min before reperfusion and continued for the first 15 min of the reperfusion period (halothane group). Halothane was titrated to an end-tidal concentration of 1.4% (Datex Capnomac Ultima, Division of Instrumentarium Corp., Helsinki, Finland) which corresponds to 1.0 MAC in rabbits.[20] In seven rabbits, the haemodynamic effects of halothane were antagonized by simultaneous infusion of noradrenaline 1.12–2.05 μg kg^{-1} min^{-1} (halothane–noradrenaline group).

DATA ANALYSIS

LV pressure, its first derivative d*P*/d*t*, AOP and stroke volume (SV) were recorded continuously on an ink-recorder (Recorder 2800, Gould Inc., Cleveland, OH, USA) and stored on a videotape recorder (SL-C 30 PS, Sony, Tokyo, Japan) using pulse code modulation (VPMD 8–12, Fa. Heim, Bergisch Gladbach, Germany) for later playback and analysis. The data were digitized using an analogue to digital converter (Data Translation, Marlboro, MA, USA) at a sampling rate of 500 Hz and processed later on a personal computer.

Haemodynamic variables

Global systolic function was measured in terms of LV peak systolic pressure (LVPSP) and maximum rate of increase in pressure (d*P*/d*t*max). Global LV end-systole was defined as the point of minimum d*P*/d*t*,[21] LV end-diastole as the beginning of the sharp upslope of the LV d*P*/d*t* tracing.

The time constant of decrease in LV isovolumic pressure (τ) was used as an index of LV diastolic function.[22] τ was calculated according to the formula:

$$P_t = P_0 \times e^{-\frac{t}{\tau}} \quad (1)$$

where P_t=instantaneous pressure; P_0=LV pressure at end-systole and τ=time constant of decrease in isovolumic pressure.

Cardiac output (CO) was calculated from stroke volume and heart rate, rate pressure product (RPP) from heart rate and LVPSP, and systemic vascular resistance (SVR) from mean AOP and CO, assuming a right atrial pressure of 0 mm Hg in the open-chest preparation.

Statistical analysis

Data are presented as mean (SEM). The effects of halothane on normal myocardium were assessed by one-way analysis of variance (ANOVA) for repeated observations. In the ischaemia–reperfusion experiments, statistical analysis was performed by two-way ANOVA for time and treatment (experimental group) effects. If an overall significance between groups was found, comparison was made for each time using one-way ANOVA followed by the Tukey–Kramer post-test when appropriate.

Results

We used 29 animals; one animal died during

Table 1 Effect of halothane on normal myocardium. In two rabbits, the effect of increasing doses of halothane was tested during α-chloralose anaesthesia. LVPSP and LVEDP=Left ventricular peak systolic and end-diastolic pressure, respectively; d*P*/d*t*max=maximum rate of increase in left ventricular pressure; CO=cardiac output; SVR=systemic vascular resistance; τ=time constant of decrease in isovolumic left ventricular pressure

		Halothane			
	Baseline	0.5 MAC (%)	0.75 MAC (%)	1.0 MAC (%)	1.5 MAC (%)
LVPSP (mm Hg)					
No. 1	95	94	87	72	57
No. 2	107	85	87	81	55
LVEDP (mm Hg)					
No. 1	4	110	112	129	139
No. 2	10	92	98	105	100
d*P*/d*t*max (mm Hg s^{-1})					
No. 1	3980	83	75	62	46
No. 2	4786	79	75	65	39
CO (ml min^{-1})					
No. 1	162	95	92	91	66
No. 2	199	101	103	104	79
SVR (mm Hg litre^{-1} min)					
No. 1	442	97	89	78	56
No. 2	450	80	87	81	55
τ (ms)					
No. 1	11	104	120	136	142
No. 2	13	111	100	121	159

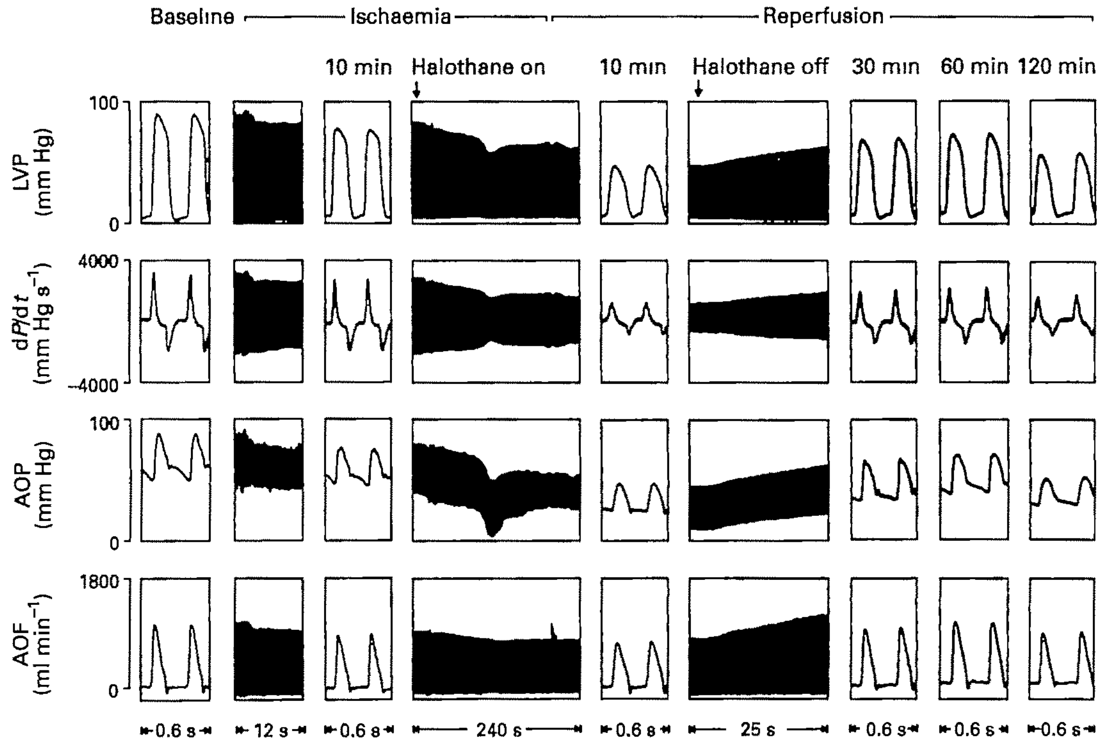

Figure 2 Analogue registration showing selected times from one experiment of the halothane treated group. LVP=Left ventricular pressure, d*P*/d*t*=rate of change of LVP, AOP=aortic pressure, AOF=aortic blood flow.

induction of anaesthesia, two died from recurrent ventricular fibrillation during coronary occlusion and two animals were excluded because the size of the area at risk was less than 0.5 g. In the remaining 24 animals, complete data sets were obtained (control group, $n=8$; halothane group, $n=7$; halothane–noradrenaline, $n=7$; halothane without coronary occlusion, $n=2$). Four animals had periods of ventricular fibrillation during coronary occlusion; two showed spontaneous defibrillation within 30 s and two needed electrical defibrillation.

HAEMODYNAMIC FUNCTION

Effects of halothane on normal myocardium

In two rabbits, the effect of halothane was tested on normal myocardium (table 1). There was a concentration dependent decrease in LVPSP, d*P*/d*t*max and SVR. CO was maintained at lower concentrations until 1.0 MAC (the concentration used in the ischaemia–reperfusion experiments) and decreased at 1.5 MAC. There was prolongation of τ, reflecting impairment of left ventricular relaxation at higher halothane concentrations.

Ischaemia–reperfusion experiments

Figure 2 shows an analogue reading of the variables in one experiment. Haemodynamic variables are

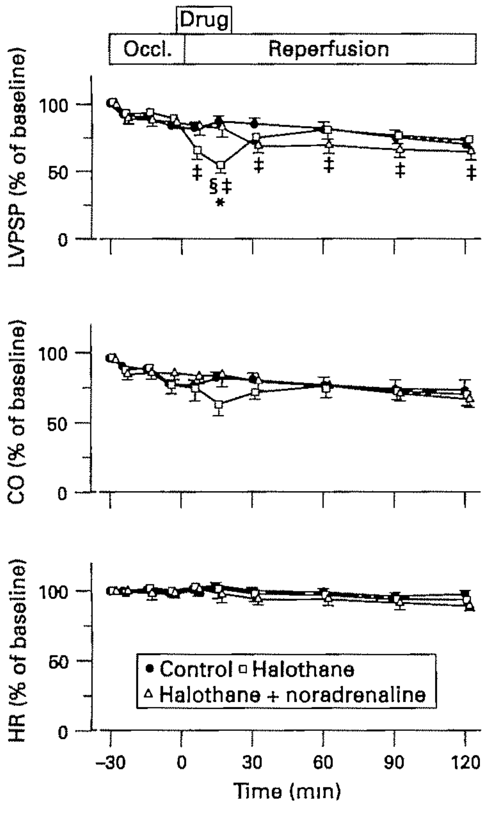

Figure 3 Line plot showing the time course of left ventricular peak systolic pressure (LVPSP), cardiac output (CO) and heart rate (HR) during the study. Data are percentage changes (SEM) from baseline. Mean baseline LVPSP was 96 (SEM 6) mm Hg in the control group ($n=8$), 91 (8) mm Hg in the halothane group ($n=7$) and 89 (7) mm Hg in the halothane–noradrenaline group ($n=7$). Baseline CO was 274 (20) ml min^{-1} in the control group, 309 (30) ml min^{-1} in the halothane group and 285 (36) ml min^{-1} in the halothane–noradrenaline group. Baseline HR was 227 (8) min^{-1} in the control group, 226 (11) min^{-1} in the halothane group and 236 (11) min^{-1} in the halothane– noradrenaline group. Occl.=Time of coronary occlusion; drug=time of halothane or halothane and noradrenaline administration, respectively. $^*P<0.05$ *vs* control; $§P<0.05$ halothane *vs* halothane–noradrenaline. $‡P<0.05$ *vs* baseline conditions.

Table 2 Haemodynamic variables during ischaemia–reperfusion experiments. Data are mean (SEM). d*P*/d*t*max=Maximum rate of increase in left ventricular pressure; SVR=systemic vascular resistance; RPP=rate pressure product; LVEDP=left ventricular end-diastolic pressure; τ=time constant of decrease in isovolumic left ventricular pressure.*$P<0.05$ compared with control group; †$P<0.05$ compared with baseline conditions; ‡$P<0.05$ compared with the halothane group

	Baseline	Coronary occlusion			Reperfusion				
		5 min (%)	10 min (%)	25 min (%)	5 min (%)	15 min (%)	30 min (%)	60 min (%)	120 min (%)
LVEDP (mm Hg)									
Control	7.5 (0.8)	145 (11)	138 (12)	143 (10)	147 (15)	149 (10)	136 (10)	137 (13)	100 (19)
Halothane	7.9 (1.1)	140 (19)	138 (18)	163 (23)	157 (15)	116 (14)	151 (31)	173 (33)	143 (22)
Halothane+ noradrenaline	7.2 (1.0)	130 (21)	114 (18)	106 (24)	192 (50)	195 (38)	103 (12)	83 (23)‡	124 (31)
d*P*/d*t*max (mm Hg s^{-1})									
Control	4635 (379)	84 (4)	83 (5)	76 (8)	64 (4)	73 (3)	72 (3)	67 (4)	61 (8)
Halothane	4039 (481)	86 (3)	90 (4)	83 (1)	43 (6)*†	37 (5)*†	60 (7)*†	63 (9)†	59 (9)†
Halothane+ noradrenaline	4149 (577)	82 (6)	81 (7)	85 (9)	51 (4)*†	49 (5)*†	50 (5)*†	50 (6)*†	47 (5)†
SVR (mm Hg litre^{-1} min)									
Control	311 (26)	102 (3)	104 (4)	98 (5)	100 (4)	96 (3)	95 (3)	94 (3)	85 (8)
Halothane	227 (24)	101 (3)	100 (3)	101 (2)	75 (7)*	62 (7)*	81 (5)*	76 (4)*	71 (6)
Halothane+ noradrenaline	234 (55)	101 (3)	97 (6)	97 (4)	85 (7)*	83 (7)*†	65 (5)*	68 (7)*	66 (8)
RPP (mm Hg min^{-1} 10^3)									
Control	22.2 (1.9)	92 (2)	92 (2)	83 (8)	84 (5)	89 (4)	85 (5)	81 (5)	70 (7)
Halothane	20.4 (2.0)	91 (3)	94 (2)	90 (8)	68 (8)	56 (8)*†	74 (5)	79 (8)	72 (1)
Halothan+ noradrenaline	21.6 (2.6)	90 (5)	85 (8)	86 (7)	86 (7)	81 (8)	67 (7)	68 (8)	60 (8)
τ (ms)									
Control	17.1 (2.0)	115 (6)	115 (7)	119 (9)	121 (11)	122 (6)	113 (4)	119 (6)	126 (15)
Halothane	17.9 (1.2)	111 (7)	121 (9)	135 (13)	175 (27)*	164 (12)*	142 (7)	132 (5)	134 (10)
Halothane+ noradrenaline	18.8 (1.9)	128 (10)	129 (8)	124 (14)	137 (16)	136 (12)	130 (7)	127 (13)	180 (29)

summarized in figure 3 and table 2. During baseline conditions, the groups were comparable in heart rate (control group 227 (8) beat min^{-1}; halothane group 226 (11) beat min^{-1}; halothane–noradrenaline group 236 (11) beat min^{-1}; $P=0.74$), LVPSP (control group 96 (6) mm Hg; halothane group 91 (8) mm Hg; halothane–noradrenaline group 89 (7) mm Hg; $P=0.76$) and CO (control group 274 (20) ml min^{-1}; halothane group 309 (30) ml min^{-1}; halothane–noradrenaline group 285 (36) ml min^{-1}; $P=0.65$). SVR tended to be higher in the control group during baseline conditions (control group 311 (26) mm Hg litre^{-1} min; halothane group 227 (24) mm Hg litre^{-1} min; halothane–noradrenaline group 234 (55) mm Hg litre^{-1} min; $P=0.18$). RPP as a major determinant of myocardial oxygen consumption was similar in all groups (control group 22.2 (1.9) mm Hg min^{-1} 10^3; halothane group 20.4 (2.0) mm Hg min^{-1} 10^3; halothane–noradrenaline group 21.6 (2.6) mm Hg min^{-1} 10^3; $P=0.31$).

In all groups, coronary occlusion was accompanied by a small reduction in LVPSP (by 13%), d*P*/d*t*max (by 20%) and CO (by 16%) (table 2, fig. 3). Consequently, SVR remained unchanged. The variables of diastolic function showed prolongation of the isovolumic relaxation phase (increase in τ by 26%) and an increase in LVEDP by 2.9 mm Hg during coronary occlusion (table 2) (all values at 25 min of coronary occlusion). In the untreated controls, reperfusion led to a small initial recovery in LVPSP (to 90% of baseline) and CO (to 88% of baseline) at 15 min of reperfusion. Halothane 1.0 MAC, given during the first 15 min of reperfusion, led to a further decline in LVPSP to 55% of baseline values and a decrease in CO (to 66%) and SVR (to 62%). After discontinuation of halothane at 15 min of reperfusion, haemodynamic variables recovered to values not different from controls. In the halothane–noradrenaline group, the decrease in CO and LVPSP during halothane administration was prevented and values were not different from controls. After discontinuation of both drugs, CO remained unchanged, but SVR, LVPSP and d*P*/d*t*max were reduced at 30 min of reperfusion to 70%, 50% and 69% of baseline values, respectively. Heart rate remained unchanged during the experiment in all groups, and consequently RPP was changed primarily in parallel with changes in LVPSP. At the end of the 120-min reperfusion period, LVPSP and CO were reduced to a similar degree in all three groups compared with baseline.

INFARCT SIZE

Mean LV weight was 5.55 (0.21) g; there were no differences between groups (data for individual animals are given in table 3). The ischaemic–reperfused area (area at risk) constituted 30.4 (2.3) % of the LV. In the control group, infarct size was 49.3 (5.7) % of the area at risk (fig. 4). Infarct size was reduced markedly in halothane treated animals (32.2 (2.9) % of the area at risk, $P<0.05$ *vs* control), and to a similar extent in the halothane–noradrenaline treated animals (30.0 (3.4) % of the area at risk, $P<0.05$ *vs* control). The relationship between the size of the area at risk and amount of infarcted tissue is shown in figure 5. The absolute size of the infarcted tissue correlated closely with the size of the area at risk in all groups (control, $r=0.98$; halothane, $r=0.69$; halothane–noradrenaline,

Table 3 Left ventricular weight, area at risk and infarct size. Data for individual rabbits

Rabbit No.	Left ventricular weight (g)	Area at risk (% of left ventricular weight)	Infarct size (% of area at risk)
Control			
1	5.4	38.0	60.2
2	4.8	24.6	47.0
3	5.0	27.3	41.6
4	6.7	28.8	64.5
5	4.1	42.5	56.4
6	6.1	16.4	14.4
7	6.4	21.5	48.4
8	6.3	43.8	61.6
Halothane			
1	4.4	36.0	34.7
2	5.0	50.3	41.9
3	6.0	47.4	19.2
4	5.6	14.1	27.5
5	6.2	18.4	39.0
6	6.3	32.0	28.8
7	7.5	33.4	34.2
Halothane+noradrenaline			
1	5.3	23.8	24.8
2	3.7	23.4	40.4
3	4.5	38.5	29.4
4	5.8	16.4	14.6
5	5.3	28.5	40.1
6	4.5	41.6	34.0
7	7.2	23.0	27.1

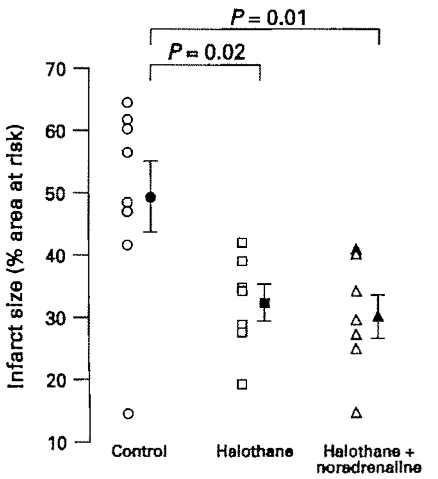

Figure 4 Infarct size as a percentage of the area at risk. Open symbols=single data points, filled symbols=mean (SEM).

r=0.81). The slope of the regression line relating infarct size and area at risk size was reduced markedly in the halothane (0.21 (0.10), $P<0.001$) and halothane–noradrenaline groups (0.37 (0.12), $P<0.01$) compared with the control group (0.86(0.07)).

Discussion

CRITIQUE OF METHODS

Variables that are considered to be important determinants for development of myocardial infarction are duration of ischaemia, collateral blood flow towards the ischaemic area, size of the area at risk and myocardial temperature during ischaemia. The rabbit has a consistently small collateral circulation[23] and therefore it was not necessary to assess collateral blood flow in the ischaemic area. The rabbit heart, however, may have other ways of supplying oxygen to parts of the area at risk, probably by diffusion or through retrograde thebesian vein circulation.[19] Consequently, there is virtually no infarction in very small areas at risk.[19] Therefore, we excluded from the analysis animals with an area at risk of less than 0.5 g. In addition, we analysed the relationship between infarct size and size of the area at risk to avoid distortion of the results by unaccounted differences in size of the area at risk between groups. Temperature was shown recently to affect infarct size even in the "normothermic range" to a large extent in the open-chest rabbit; a change in infarct size of approximately 10% for each 1 °C was reported.[24] Therefore, in this study, temperature was measured inside the pericardium and kept within a narrow range of 38.5±0.3 °C.

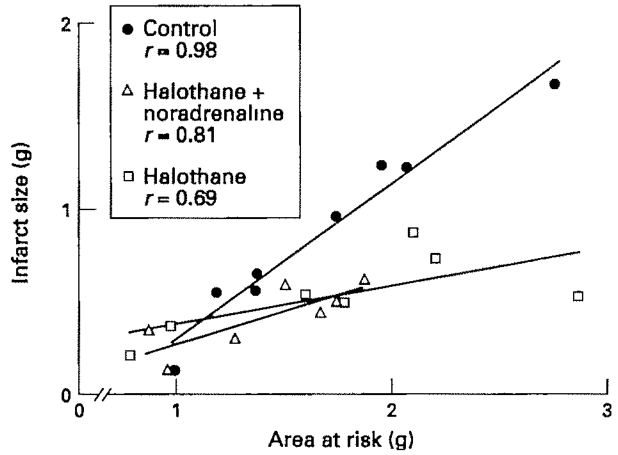

Figure 5 Scatterplot of the relationship between infarct size and size of the area at risk. Slopes of regression lines were smaller in the halothane ($P<0.001$) and halothane–noradrenaline groups ($P<0.01$). Control group, $y=0.86$ (SEM 0.07) $x-0.54$ (0.13); halothane group, $y=0.21$ (0.10) $x+0.18$ (0.19); halothane–noradrenaline group, $y=0.37$ (0.12) $x-0.09$ (0.17).

All experiments were carried out during anaesthesia with α-chloralose. This type of anaesthesia maintains near normal cardiovascular reflexes comparable with the awake state[25] and is a classical anaesthetic for physiological and pharmacological experiments.[26] An anti-ischaemic action of α-chloralose has not been found,[27–29] but we cannot completely exclude interference with reperfusion injury in our study.

As the danger of impending hypercontracture in the reoxygenated myocardial cell is evoked by reactivation of mitochondrial energy production,[30] a protective substance should be present at the onset of reperfusion. In anoxic reoxygenated rat cardiomyocytes, we found that intracellular calcium homeostasis recovered within 5 min[10] and after this period administration of halothane could be discontinued without danger of hypercontracture. For these reasons, we administered halothane 3 min before reperfusion in order to have a stable end-tidal concentration corresponding to 1.0 MAC at the onset of reperfusion, and discontinued halothane after 15 min of reperfusion. Because the rabbit has virtually no collateral circulation[23] allowing halothane to reach the ischaemic myocardium, and because there was only a short period of administration during the last 3 min of ischaemia, a potential anti-ischaemic effect is unlikely to have contributed substantially to the protection.

INTERPRETATION OF RESULTS

Reperfusion of ischaemic myocardium after temporary coronary occlusion initiates structural and biochemical changes that limit the amount of potentially salvageable myocardium (reperfusion injury).[12] In previous *in vitro* studies, we found that halothane markedly reduced the oxygen paradox type of reperfusion injury in isolated hearts[8] and isolated cardiomyocytes.[9] The oxygen paradox was described originally for hypoxic-perfused and reoxygenated isolated hearts and is characterized by abrupt development of hypercontracture and cytolysis after re-supply of oxygen.[31] Cellular hypercontracture depends on several factors: re-supply of ATP by reactivation of oxidative phosphorylation and cycles of transient release and reuptake of Ca^{2+} by the sarcoplasmic reticulum.[32] These calcium cycles trigger uncontrolled activation of the contractile elements,[11] leading finally to cytolysis and cell death, most likely as a result of mutual mechanical disruption of the cells.[33 34] In isolated anoxic reoxygenated cells, halothane prevented these Ca^{2+} oscillations by an action on the Ca^{2+}-dependent–Ca^{2+}-release channel of the sarcoplasmic reticulum.[9 10] This study has extended these findings to the situation of reperfusion after regional myocardial ischaemia *in vivo*, leading to a marked reduction in myocardial infarct size when given during the initial reperfusion period. Other cellular mechanisms affected by halothane are calcium influx via voltage-dependent calcium channels and inhibition of the Na^+–H^+ exchange mechanism.[35] The former is important for the negative inotropic effect of halothane in normal myocardium,[36] but may play only a minor role in the development of lethal reperfusion injury.[37] The latter mechanism has been shown to protect against reperfusion injury[38] by preserving intracellular acidosis and preventing pathological calcium cycling.[11] However, in isolated anoxic reoxygenated cells,[10] recovery of intracellular acidosis was not prolonged in the presence of halothane, suggesting that inhibition of the Na^+–H^+ exchanger by halothane is of minor importance during reperfusion.

In addition to the direct influence on the reperfused myocardium, the haemodynamic effects of halothane during the initial 15 min of reperfusion could have influenced the extent of myocardial damage. During this period, halothane reduced LVPSP and RPP, as a variable of myocardial oxygen demand, by 35% and 34%, respectively. These changes in LVPSP were similar to the effects seen in rabbits without ischaemia–reperfusion. While CO was nearly maintained at 1.0 MAC of halothane in normal hearts, the same concentration was accompanied by a reduction in CO (by 18%) in the presence of regional ischaemia–reperfusion. The effects on myocardial reperfusion injury that result from these changes in ventricular loading conditions and the reduction in myocardial inotropy are not known exactly and experimental data are contradictory. In an *in vivo* dog heart preparation, with 2 h of coronary occlusion the protective effect of 100% ventricular unloading by cardiopulmonary bypass for a 4-h reperfusion period was investigated and resulted in 50% reduction in infarct size.[39] In isolated rabbit hearts, however, complete ventricular unloading had no effect on infarct size.[40] To exclude possible effects of a reduction of ventricular loading conditions by halothane during the initial reperfusion period, we antagonized the negative inotropic and vasodilator effects by continuous infusion of noradrenaline during halothane administration. This treatment effectively prevented the haemodynamic effects during administration of halothane, but there was a small decrease in SVR and, consequently, LVPSP after discontinuation of both drugs. However, these changes were small (LVPSP decreased by 22%) and were too late during reperfusion to explain the marked reduction in infarct size, because lethal reperfusion injury starts with resumption of mitochondrial energy production at the early onset of reperfusion.[30] In addition to its global haemodynamic effects, noradrenaline also acts as a coronary vasoconstrictor. Although coronary flow was not measured in this study, significant coronary vasoconstriction produced by noradrenaline is unlikely because coronary vasoconstriction can be expected to increase infarct size, and in our study the reduction in infarct size by halothane was unchanged by the presence of noradrenaline. In conclusion, it is unlikely that the haemodynamic effects of halothane contributed to the observed myocardial protection.

In vivo, the activated leucocyte is an additional potential cause of (late) lethal reperfusion injury.[41] Although leucocyte activation and accumulation is a consequence of initial state of tissue injury, leucocytes may cause further injury by synthesizing and releasing a variety of mediators, including oxygen-derived free radicals and oxidants.[41] By plugging capillaries, they are thought to play an important role in the "delayed no-reflow phenomenon",[42] resulting in persistent ischaemia. Consequently, leucocyte depletion during reperfusion reduces the "no-reflow" and infarct zones in dog.[43] Halothane anaesthesia may reduce leucocyte activity *in vivo*.[44 45] A reduction in post-ischaemic adhesion of (human) leucocytes in the coronary system of guinea pigs was shown recently in the presence of halothane *in vitro*.[46] Actions on leucocyte activation may have contributed to the myocardial protection observed in this study.

Myocardial reperfusion injury may occur in a variety of clinical settings such as thrombolysis, percutaneous balloon angioplasty and after periods of cardiac arrest during heart surgery with cardiopulmonary bypass. Using isolated rat hearts, it was possible to show that administration of halothane during reperfusion conferred additional cardiac protection after cardioplegic arrest.[47] Further studies must show if the cardioprotective effects of halothane against reperfusion injury are clinically significant.

In summary, we found that treatment with 1.0 MAC of halothane during the early reperfusion period after regional myocardial ischaemia reduced markedly the extent of myocardial infarction *in vivo*. The reduction in infarct size was similar if negative inotropy and vasodilatation were antagonized by infusion of noradrenaline. Therefore, the protection was probably not caused by the haemodynamic effects of halothane, but by a specific action on the reperfused myocardium.

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Effects of alfentanil on cerebral haemodynamics in an experimental model of traumatic brain injury†

M. J. SOUTER, P. J. D. ANDREWS, I. R. PIPER AND J. D. MILLER

Summary

Alfentanil is reported to increase intracranial pressure (ICP) after neurotrauma. A direct cerebral vasodilator effect has been postulated. We studied 17 Sprague–Dawley rats allocated to one of three groups. Animals were anaesthetized and their lungs ventilated, and arterial pressure, ICP and/or regional cerebral blood flow (CBF) measurements were undertaken. Group 1 (n=6) received a severe closed head injury while group 2 (n=5) received no injury. ICP and mean arterial pressure (MAP) were measured before, during and after rapid infusion of alfentanil 250, 500 and 750 μg kg^{-1}. CBF was measured by hydrogen clearance before rapid infusions and at 30-min intervals after starting a subsequent slow infusion of alfentanil 500 μg kg^{-1} h^{-1}. Group 3 (n=6) underwent CBF measurement only, for comparison with those of groups 1 and 2. They received an injury but no alfentanil. ICP or MAP values did not differ significantly between groups 1 and 2. Rapid i.v. doses of alfentanil produced increases in ICP and reductions in MAP. ICP changes were consistent with a drug effect (P<0.001) but were small. Reductions in MAP were significant (P<0.05) and preceded changes in ICP. CBF values were similar and unaffected by slow alfentanil infusion in groups 1 and 2, and did not differ significantly between groups 1 and 3. We conclude that alfentanil did not appear to exert a direct effect on the cerebral circulation. Changes in ICP after rapid infusion were secondary to reductions in SAP. Slow infusion did not cause such changes. (*Br. J. Anaesth.* 1997; **79**: 97–102).

Key words
Analgesics opioid, alfentanil. Brain, injury. Brain, blood flow. Brain, intracranial pressure. Rat.

Cerebral perfusion pressure (CPP) is defined as the difference between mean arterial pressure (MAP) entering the skull and intracranial pressure (ICP). ICP can be increased (greater than 20 mm Hg) after trauma by a change in volume of the cranial contents, particularly haemorrhage, swelling secondary to trauma and increased cerebral blood volume (CBV).

In 1989 Marx and colleagues reported that a rapid infusion of alfentanil increased lumbar CSF pressures.[1] He considered that this reflected increased ICP and advised against the use of alfentanil in intracranial hypertension.

In 1992 Moss reported a series of five patients with normal pressure hydrocephalus, all of whom suffered increases in ICP in response to rapid infusions of alfentanil 1 mg.[2] Two of these five patients had only small changes in arterial pressure and the author considered that the effect resulted from a direct cerebral vasodilator action of alfentanil, advising against its use in patients with increased ICP.

We had not observed such a response during administration of alfentanil in our intensive therapy unit (ITU) and, given the widespread use of alfentanil in neuroanaesthesia and ITU, we wished to investigate this phenomenon prospectively in a controlled environment. The aims of this study were to examine the net change in the components of cerebral perfusion (ICP and MAP) in response to rapid i.v. infusions and to assess any change in blood flow or vascular resistance in the brain in response to slow infusions. In this manner, we hoped to examine the two methods by which alfentanil is usually administered. An animal study in a laboratory environment was chosen in order to standardize the cerebral injury and control other physiological variables.

Materials and methods

The study was approved by the Home Office under project licence 60/01228.

We studied 17 male Sprague–Dawley laboratory rats, weighing 320–400 g, allocated to one of three groups. Group 1: rats received a head injury and infusions of alfentanil (n=6); group 2: rats received no injury but did receive alfentanil (n=5); group 3: rats received a head injury alone (n=6).

Rats had free access to food and water until the morning of the experiment. The study sequence consisted of anaesthesia, surgical preparation, insertion of monitoring, and injury or sham.

M. J. SOUTER, MB, CHB, FRCA, P. J. D. ANDREWS, MD, FRCA, I. R. PIPER, PHD, J. D. MILLER, MD, PHD, FRCS, FACS, FRCP(E), University Department of Clinical Neurosciences, Western General Hospital, Crewe Road South, Edinburgh EH4 2XU.
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Animals received brief exposure to halothane in oxygen and nitrous oxide, which allowed i.p. injection of a mixture of alpha-chloralose and urethane (80 mg+800 mg kg^{-1}, approximately 1 ml/100 g weight). This latter injection provided anaesthesia for the duration of the experiment.

After intubation (16-gauge cannula) and subsequent paralysis with pancuronium 2 mg kg^{-1}, positive pressure ventilation was commenced to normocapnia (Pa_{CO_2} 4.5–5.5 kPa) by the Harvard Rodent ventilator (Harvard Apparatus Ltd, Kent, UK). Hartmann's solution was given i.v. at 2 ml h^{-1} throughout the study.

Arterial pressure was monitored via a cannula in the femoral artery, permitting regular arterial blood-gas analysis. The femoral vein was also cannulated via the same incision. Then, 45–60 min after induction of anaesthesia, the animal received an injury or sham injury, as detailed below. It was then placed in a stereotactic frame, and 2-mm diameter burrholes were drilled under direct microscopy. For ICP monitoring, the lateral ventricle was cannulated via a burrhole under direct microscopy, using a Sprotte 24-gauge spinal needle (Rusch Direct, High Wycombe, Buckinghamshire, UK). This was accomplished using a pressure monitored loss of resistance to mechanical fluid infusion to indicate penetration of the ventricle.

Platinum hydrogen electrodes (150 μm) were inserted into the sensorimotor cortex at a standardized depth of 1 mm. After 30 min, baseline cerebral blood flow (CBF) measurements were obtained, at a time corresponding to 75–90 min after injury. Measurement was made using the hydrogen clearance technique, saturating the rat with inspired hydrogen (10%) and measuring the decrease in current at the cortical electrodes as hydrogen was cleared from cerebral tissues.[3]

The exponential washout curve obtained was transformed logarithmically, and the flow derived from a standardized analysis of the initial rate of decline, representing mixed cortical gray and subcortical white matter blood flow.[4] The first flow measurements were discarded and subsequent flow was recorded.

Physiological variables (i.e. systolic and diastolic arterial pressures, ICP) from data monitoring (Kontron Colormon, Kontron Instruments Ltd, Watford, UK) were downloaded to a computer every 15 s and continuously to chart recorders. Subsequently, rapid i.v. infusions of alfentanil (Janssen Pharmaceutical Ltd, Grove, Wantage, Oxon, UK) 250, 500 and 750 μg kg^{-1} were given. This represents low, moderate and high dosage for the rat.[5-7]

After each dose, MAP and ICP were allowed to return to pre-injection levels or plateau for a period of 5 min before the next dose was given. The rationale of using increasing doses was not to characterize a dose–response curve but to obtain an effect on ICP and MAP. After three rapid i.v. doses, the animal received continuous infusion of alfentanil 500 μg kg^{-1} h^{-1}. CBF was measured after 30 min and repeated at intervals of 30 min.

If CBF was increased, there was an optional arm of the study to give naloxone 40 μg kg^{-1} and then immediately repeat CBF measurements to assess any opioid receptor-mediated effect. This was only required twice and did not prove useful.

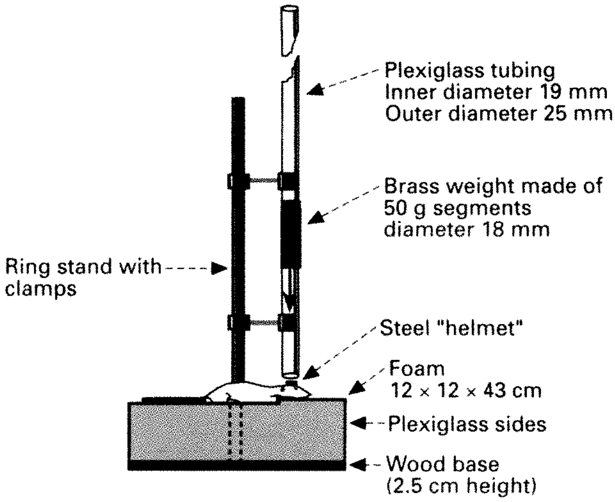

Figure 1 Schematic diagram of the weight drop injury model.

Injury was produced using the impact acceleration model developed by Marmarou and colleagues in Richmond, Virginia and represents a severe brain concussion, both clinically and pathologically.[8] In this model the skull is exposed and a metal disc cemented in the midline between the bregma and lambda. This is considered as a "crash helmet" to protect against skull fracture and ensure diffuse injury. A 450-g weight is then dropped a distance of 2 m onto the helmet (fig. 1).

A characteristic reduction in MAP is observed, the duration of which relates to the severity of the injury.[9] After recovery of MAP from this primary injury, usually within 15 min, ICP was measured as detailed above, and hydrogen electrodes placed.

Data were subjected to analysis of variance (ANOVA) and the Kruskal–Wallis tests for significance testing, and are expressed as mean (SEM) with 95% confidence intervals (CI).

Results

ICP AND MAP

Changes in pressure

Results are categorized for dose of alfentanil and presence or absence of injury, for the first two groups (fig. 2).

Examination of ICP and MAP recordings after rapid infusions revealed that MAP decreased by a mean of 15 mm Hg (SEM 3.3; 95% CI 5.6–23.7), in association with a mean increase in ICP of 5 mm Hg (0.5; 95% CI 3.7–6.6), producing an overall decrease in CPP of 20 mm Hg (3.4; 95% CI 11.2–29.8).

Alfentanil 250 μg kg^{-1}. Group 1 (injury), who received alfentanil 250 μg kg^{-1}, showed a reduction in MAP of 21 mm Hg (8.4; 95%CI −0.6 to 42.6) with an increase in ICP of 7 mm Hg (1.8; 95% CI 2.6–12.1). Group 2 (sham) had a reduction in MAP of 19 mm Hg (13.4; 95% CI −17.9 to 56.5) with an

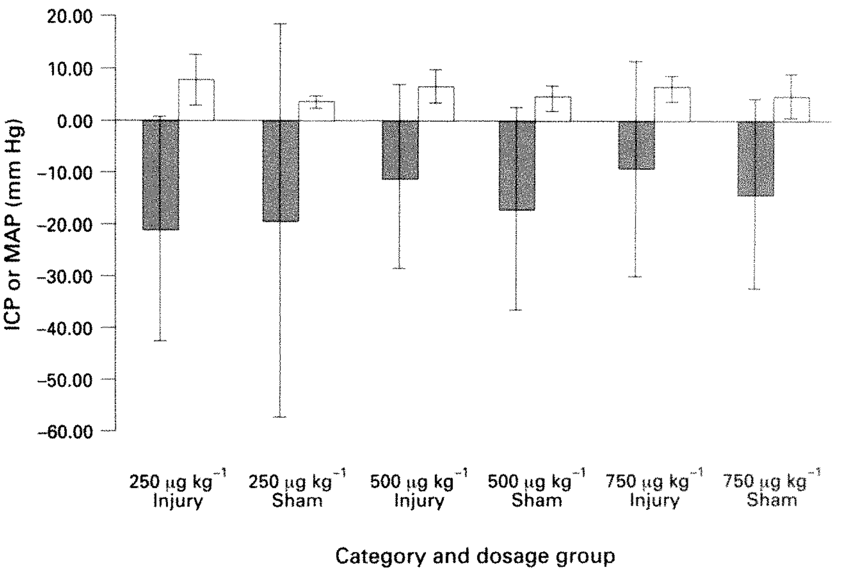

Figure 2 Effect of alfentanil 250, 500 and 750 µg kg^{-1} on ICP (☐) and MAP (▨) in the presence or absence (sham) of injury (mean, 95% confidence intervals).

increase in ICP of 3 mm Hg (0.4; 95% CI 2.1–4.5).

Alfentanil 500 µg kg^{-1}. MAP was reduced by 11 mm Hg (6.7, 95% CI −6.7 to 27.9) and ICP increased by 6 mm Hg (1.2; 95% CI 3.4–9.4) in group 1, while group 2 showed a reduction in MAP of 17 mm Hg (6.9; 95% CI −2.2 to 36) and an increase in ICP of 4 mm Hg (0.9; 95% CI 1.9–6.7).

Alfentanil 750 µg kg^{-1}. In group 1, MAP was reduced by 9 mm Hg (7.9; 95% CI −11.2 to 29.5) and ICP was increased by 6 mm Hg (0.9; 95% CI 3.9–8.5). Group 2 showed reductions in MAP of 14 mm Hg (6.5; 95% CI −4.3 to 32) and increases in ICP of 5 mm Hg (1.5; 95% CI 0.6–8.9).

Changes in ICP were significant ($P<0.001$) throughout the study. Changes in MAP were also significant ($P<0.05$), but were clinically more relevant in that they produced greater net effects on CPP. There were no significant differences between dose or injury groups.

Changes with time

In order to assess which effect had precedence, we examined: (i) time taken from injection until changes were first observed in MAP and ICP; (ii) time until the peak of that change; and (iii) time until recovery from that change.

The initial point of change was defined as the beginning of a pressure transient that at its extreme exceeded two SD of the averages of 10 measurements preceding the initial point of change. The point of recovery was defined as the end of a transient that returned to baseline levels and remained stable thereafter.

(i) Time taken from injection until changes were first observed in MAP and ICP

Averaging all groups, MAP was affected at 13 s (0.6; 95% CI 12–15) and ICP at 22 s (2; 95%CI 16.6–27).

Alfentanil 250 µg kg^{-1}. In group 1, MAP was affected at 13 s (1; 95% CI 10.6–16) and ICP at 14 s (0.5; 95% CI 13.2–15.8). Group 2 experienced an effect on MAP at 15 s (0.2, CI 14–15.2) and on ICP at 27 s (5.6; 95% CI 12.5–41.4) ($P<0.05$).

Alfentanil 500 µg kg^{-1}. Changes in MAP for group 1 were first seen at 11 s (2.4; 95% CI 4.7–17.3) and at 18 s (3.1; 95% CI 10.4–26.2) for ICP. In group 2, changes in MAP started at 15 s (0.2; 95% CI 14.7–15.7) and at 24 s (6; 95% CI 8.6–39.4) for ICP.

Alfentanil 750 µg kg^{-1}. MAP changed in group 1 at 11 s (2.2; 95% CI 5.9–17.1) and ICP at 22 s (3.6; 95% CI 12.7–31.3), while MAP in group 2 changed

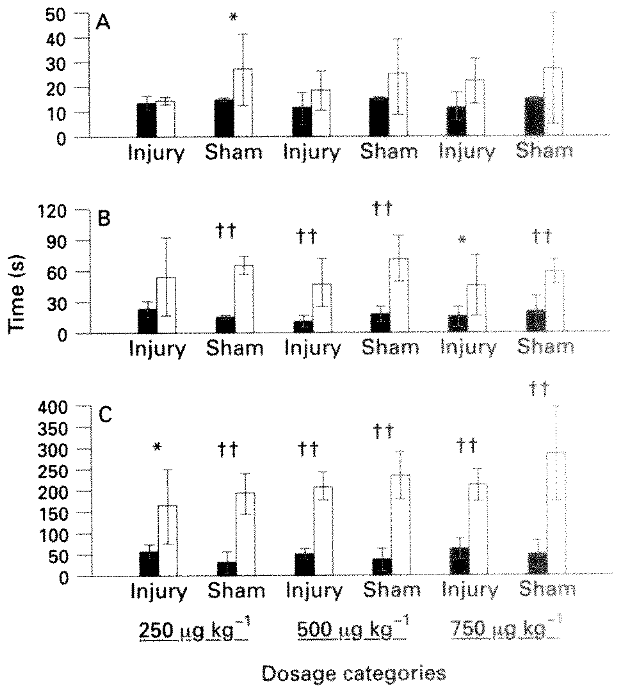

Figure 3 Intervals of changes in MAP (■) and ICP (☐) after rapid infusion of alfentanil 250, 500 and 750 µg kg^{-1} in the presence or absence (sham) of injury (mean, 95% confidence intervals). A: Time to initial changes; B: time to maximum changes; and C: time to recovery. $^{*}P<0.05$; $^{††}P<0.01$.

Table 1 Cerebral blood flow measurements ($\text{ml}\ 100\ \text{g}^{-1}\ \text{min}^{-1}$) in the three groups (mean (95% confidence intervals))

	Time from injury/sham(h)				
	1	2	2.5	3	3.5
Group 1	34.6	36.3	37.6	39.2	
(injury plus alfentanil)	(20.8–48.4)	(19.6–53.1)	(14.3–60.9)	(15.7–62.7)	
Group 2	33.7	37.1	38.3	31.7	34.7
(sham plus alfentanil)	(27.9–39.5)	(25.0–49.2)	(24.2–52.4)	(14.9–48.4)	(2.9–66.6)
Group 3	39.1	59.6	58.5	65.9	
(injury alone)	(30.6–47.7)	(41.8–77.4)	(40.3–76.7)	(44.1–87.7)	

at 15 s (0.2; 95% CI 14.3–15.3) and ICP at 27 s (8.7; 95% CI 4.5–49.5).

There were no significant differences between dose or injury groupings. For all groups, MAP was affected before ICP, irrespective of dose or injury.

(ii) Time until peak of change

The effect on MAP preceded the effect on ICP, with MAP peaking at 17 s overall (1.5; 95% CI 13.5–21.2) and ICP at 57 s (4.2; 95% CI 46.4–67.8).

Alfentanil 250 μg kg^{-1}. MAP changes in group 1 peaked at 22 s (3.6; 95% CI 13.3–31.7) and ICP at 55 s (14.8; 95% CI 16.9–93.1). In group 2, MAP peaked at 15 s (0.3; 95% CI 14.2–15.8) and ICP at 66 s (3.7; 95% CI 56.6–75.4) ($P<0.01$).

Alfentanil 500 μg kg^{-1}. MAP changes for group 1 peaked at 11 s (2.4; 95% CI 4.7–17.3) and ICP at 48 s (9; 95% CI 25.2–71.5) ($P<0.01$). In group 2, MAP peaked at 15 s (0.3; 95% CI 14.2–15.8) and ICP at 72 s (8.7; 95% CI 49.5–94.5) ($P<0.01$).

Alfentanil 750 μg kg^{-1}. MAP changes in group 1 peaked at 15 s (3.9; 95% CI 5.5–25.5) and ICP at 46 s (11.2; 95% CI 16.9–74.4) ($P<0.05$). In group 2, MAP peaked at 21 s (6; 95% CI 5.6–36.4) and ICP at 60 s (4.7; 95% CI 47.8–72.2) ($P<0.01$).

There was no relationship with dose or injury as there were no significant differences between these groupings.

(iii) Time until recovery from changes

This pattern was repeated with time taken from injection until values return to normal. MAP returned to normal by 45 s overall (4.1; 95% CI 34–55) while ICP remained above baseline for 214 s (11.9; 95% CI 183.7–244.8).

Alfentanil 250 μg kg^{-1}. MAP values for group 1 returned to normal at 45 s (12.8; 95% CI 12–78) and ICP at 163 s (33.9; 95% CI 76.3–250.4) ($P<0.05$). In group 2, MAP returned to normal at 52 s (7.5; 95% CI 33.2–71.8) and ICP at 192 s (18.6; 95% CI 144.2–239.9) ($P<0.01$).

Alfentanil 500 μg kg^{-1}. MAP values in group 1 returned to normal at 28 s (9.2; 95% CI 4.4–51.6) and ICP at 209 s (12.5; 95% CI 177.1–241.2) ($P<0.01$). In group 2, MAP returned to normal at 48 s (5.6; 95% CI 33.6–62.4) and ICP by 234 s (22; 95% CI:177.3–290.7) ($P<0.01$).

Alfentanil 750 μg kg^{-1}. Group 1 MAP values returned to normal at 35 s (10.7; 95% CI 7.4–62.6) and ICP at 213 s (14.8; 95% CI 175.2–251.4) ($P<0.01$). In group 2, MAP returned to normal at 60 s (9.5; 95% CI 35.6–84.4) and ICP at 285 s (43; 95% CI 174.6–395.4) ($P<0.01$).

CEREBRAL BLOOD FLOW

Analysis of cerebral blood flow (CBF) at staged times revealed no significant differences between groups 1 and 2 (table 1). Both groups demonstrated little variation in CBF in the 3 h after injury. Comparison between groups 1 and 3 (injury–no alfentanil) showed lower CBF for the alfentanil group (table 1).

At 1 h after injury, group 3 had similar CBF values to alfentanil-treated animals, but by 3 h after injury, CBF increased to a positive difference of 26.7 $\text{ml}\ 100\ \text{g}^{-1}\ \text{min}^{-1}$ but this was not statistically significant.

Discussion

Since the study of Marx and colleagues,[1] when reductions in arterial pressure and increases in lumbar CSF pressure were observed after rapid infusion of alfentanil and sufentanil in patients with supratentorial tumours, there have been various opinions on the effects of alfentanil on cerebral haemodynamics.

Alfentanil had been demonstrated previously to be satisfactory when given by slow i.v. infusion with midazolam, reducing ICP and producing less decreases in MAP and right atrial pressure than fentanyl, suggesting a discrepancy between rapid and slow infusion effects.[10]

Rapid infusions of fentanyl, sufentanil and alfentanil produced negligible effects on brain retractor pressure, which is related to parenchymal pressure.[11] Decreases in MAP and CPP were, however, noted and appeared to be related to the dose of alfentanil. This was demonstrated in both control and injured animals receiving rapid infusions during our study.

A similar effect on MAP was demonstrated by Schregel and colleagues when examining the effect of alfentanil on CBF velocity measured using transcranial Doppler ultrasound.[12] A transient decrease in MAP, coupled with a decrease in mean flow velocity and an increase in pulsatility index, occurred. Subsequently, Moss reported increases in ICP after administration of alfentanil 1 mg by rapid infusion in five patients with normal pressure hydrocephalus who were undergoing pressure compliance tests.[2] The author deduced that because of limited changes in MAP in two of the patients, in contrast with the large reductions in MAP seen in the three other patients, that it was unlikely that the increase in ICP was in response to compensatory cerebral vasodilatation from systemic hypotension. He considered that it was caused by a direct vasodilator effect of alfentanil on the cerebral vessels. However, MAP was monitored only on a minute-by-minute basis using arm cuff arterial pressure measurement which would not detect more transient decreases in MAP. Nevertheless, he advocated discontinuation of rapid infusion of alfentanil in patients at risk of increases in ICP. This view was supported by similar case reports.[13 14]

This supposition of a direct vasodilator effect is in contrast with the results we have obtained, which clearly illustrate an effect on MAP that precedes any changes in ICP. Our data demonstrated that transient decreases in MAP had returned to baseline levels by 1 min, and the frequency of arterial pressure monitoring used by Moss was unlikely to detect such a decrease in MAP and would only demonstrate a persistent increase in ICP of slower onset and longer duration. It has been suggested that the difference in duration between cerebral and systemic vasodilatation is caused by venous outflow resistance, where increases in ICP contribute not only to reductions in perfusion through cerebral inflow vessels, but also to partial or complete occlusion of the large cerebral veins draining the base of the skull causing an increase in cerebral venous volume.[15]

The presumed direct effect was contradicted by another study that year in which children anaesthetized for CSF shunt surgery were given increasing rapid infusions of alfentanil 10, 20 and 40 $\mu g\ kg^{-1}$ i.v. which caused decreases in heart rate, MAP and CPP with all doses.[16] Using shunt as the pressure monitor, ICP did not change from baseline. These children were on the steep slope of the intracranial volume–pressure curve where cerebral volumetric compensatory mechanisms were exhausted and vasodilatation was likely to cause an increase in ICP.

Similarly, rapid infusions of alfentanil 25 and 50 $\mu g\ kg^{-1}$ i.v. were given to neurosurgical and orthopaedic patients, with neurosurgical patients receiving phenylephrine concurrently. Despite this, MAP decreased in both groups with the higher dose, with a clinically insignificant 2-mm Hg increase in ICP in neurosurgical patients.[17] Middle cerebral artery (MCA) velocities decreased in the orthopaedic high-dose group but not in the low-dose group.

No changes in MCA velocity were seen in neurosurgical patients or changes in oxygen extraction, suggesting there was no effect on CBF. This is in keeping with our results, which demonstrated no significant effect on actual CBF when alfentanil was given by slow infusion, and suggests that alfentanil does not exert a primary vasodilator effect on the cerebral vasculature. The transcranial Doppler study by Schregel and colleagues also showed that the cross-sectional area of the MCA was unaffected by alfentanil, suggesting no cerebral vasodilator effect.[12] This was supported further by work measuring the diameter of cerebral arterioles in piglets in response to alfentanil and other opioids. Vasoconstriction rather than vasodilatation occurred. This was attenuated by naloxone and was dose dependent.[18]

This is an interesting observation in relation to the reduction in CBF seen in our study when comparing injured animals receiving a slow infusion of alfentanil with injured animals receiving no alfentanil. Although the differences were not statistically significant, it is tempting to speculate that alfentanil may have attenuated the pathological increase that occurred after head injury alone.

Our study demonstrated that alfentanil reduced CPP when administered by rapid infusion. The likely mechanism of effect on cerebral perfusion, as illustrated by our data, is not via a directly mediated effect on the cerebral circulation, but rather a secondary cerebral vasodilator response to an induced reduction in systemic MAP, resulting in an increase in ICP. This secondary effect persisted beyond the initial reduction and may have appeared as a primary event, depending on the frequency of monitoring.

The important consequence was a reduction in CPP, rather than an effect on ICP, and was of transient duration. Although previous reports have commented on simultaneous reductions in MAP and increases in ICP, there is little information on the duration of effect on CPP. Our data would indicate that it is not prolonged.

There was no evident effect on CBF when alfentanil was given by slow infusion, suggesting that alfentanil does not induce direct vasodilatation.

While recognizing that these results arise from a laboratory model of brain injury, we consider that they are applicable to the human head-injured patient, given that mammalian haemodynamic responses are broadly similar and that dose ranges for the rat were used which are comparable in efficacy with those used in humans.

We consider that alfentanil should not be given by rapid infusion in patients with neurotrauma, especially in view of possible haemodynamic instability. There is no evident contraindication to the use of alfentanil when given by slow i.v. infusion.

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Quantitative study of Lowe's square-root-of-time method of closed-system anaesthesia

J. M. Couto da Silva, W. W. Mapleson and M. D. Vickers

Summary

Intermittent injection of liquid anaesthetic into a closed breathing system is particularly suitable in countries with limited resources. A method of calculating appropriate times and magnitudes of the injected doses was described by Lowe but the method has never been assessed rigorously. Such an assessment was the purpose of this study. The technique was used in a double-blind, randomized comparison of halothane, enflurane and isoflurane in oxygen–air, with 20 ASA I or II patients in each group, undergoing superficial or abdominal surgery. The prescribed times of injection were adhered to, but the doses, after the first two, were adjusted to maintain systolic arterial pressure within 20% of the reference preoperative value. Partial pressures of the anaesthetics were monitored but concealed from the investigator–anaesthetist. The mean doses found necessary for each anaesthetic were within 33% of those calculated to produce 1.3 MAC. However, end-tidal partial pressure (just before each dose) stabilized at a steady level of only 0.97, 0.42 and 0.77 MAC for halothane, enflurane and isoflurane, respectively. Recovery from enflurane was much more rapid than that from the other agents but no patient admitted to any dreams. We conclude that the rate of uptake of anaesthetic declines more slowly than predicted and that the patients receiving enflurane were less deeply anaesthetized because the greater hypotensive effect of enflurane led to the use of smaller doses. (*Br. J. Anaesth.* 1997; **79**: 103–112).

Key words
Anaesthetic techniques, low flow. Anaesthetic techniques, closed-system Anaesthetics volatile, halothane. Anaesthetics volatile, enflurane. Anaesthetics volatile, isoflurane.

Lowe,[1] and subsequently Lowe and Ernst,[2] have argued theoretically that if a "priming dose" of liquid anaesthetic is injected into a closed anaesthetic breathing system at 0 min, and a "unit dose" at 1^2, 2^2, 3^2 (1, 4, 9), etc. min, arterial partial pressure of the anaesthetic increases rapidly and then stays constant. Specifically, the priming dose should bring the gas in the breathing system and arterial blood to the specified partial pressure, often taken to be 1.3 MAC; subsequent unit doses should supply uptake to the tissues that occurs during the interval until the next dose. The argument is supported by calculations by Mapleson.[3] It is acknowledged[2] that different patients need different concentrations and therefore different doses, and that these are tailored to the patient by a competent anaesthetist. This technique of anaesthesia is particularly suitable for developing countries.

However, there are two gaps in our knowledge of the method. First, although a closely related method has been studied,[4] the Lowe method has never been subjected to rigorous quantitative assessment. Second, when Couto da Silva and others[5–8] used this method in unblinded studies with halothane, enflurane and isoflurane, they found that the injected volumes of enflurane required to maintain a constant systolic arterial pressure (SAP) were much less than the 1.3-MAC unit dose, and that recovery was more rapid with enflurane than with halothane or isoflurane. However, they could not identify the cause of the discrepancies because they were unable to measure anaesthetic partial pressure.

Therefore, this study was designed to answer four questions on the clinical use of Lowe's method. (1) Are the required doses, and the resulting arterial partial pressures, consistent with Lowe's theory? (2) Can the findings of Couto da Silva be replicated in a double-blind study? (3) If so, can the cause of the discrepancy between agents be elucidated? (4) Whatever the answer to these three questions, does Lowe's method produce satisfactory anaesthesia?

Patients and methods

STUDY DESIGN

On the basis of an exploratory study,[9] 60 adult patients were allocated randomly by a computer program[10] to be anaesthetized with halothane, enflurane or isoflurane (20 patients per group).

J. M. Couto da Silva*, PhD, FACA, M. D Vickers, MB, BS, FRCA, W. W. Mapleson, DSc, FInstP, FRCA (Hon), Department of Anaesthetics and Intensive Care Medicine, University of Wales College of Medicine, Cardiff CF4 4XN. Accepted for publication: January 26, 1997.

*Present address: Department of Anaesthesiology, University of Brasília, Brasília, Brazil.

Correspondence to W. W. M.

Patient and anaesthetist were blinded to the agent used. Inclusion criteria were: ASA status I or II, age 20–65 yr, and upper or lower abdominal, or superficial surgery lasting at least 75 min. Exclusion criteria were: halothane anaesthesia within the previous 3 months; heavy intake of alcohol; cardiac, pulmonary, neurological or renal disease; patients receiving any drug that could alter the MAC of the anaesthetics; and pregnancy. Informed, verbal consent was obtained from all patients and the study was approved by the relevant local research Ethics Committee.

Patients were anaesthetized according to the square-root-of-time method, with a specified partial pressure of 1.3 MAC, and as practised in developing countries except as follows. To assist in blinding, the dose at 0 min was 2 ml for all three anaesthetics and that at 1 min was 1, 1.5 or 2 ml according to body weight (less than 60 kg, 60–75 kg and greater than 75 kg, respectively). These doses were justified by the exploratory study.[9] The prescribed times of subsequent doses were adhered to, but the doses were chosen by the anaesthetist as those most likely to maintain or regain the required depth of anaesthesia. "Normal" depth was defined primarily as an SAP within 20% of a reference preoperative SAP, with some allowance for other clinical signs (heart rate, sweating, tears). The times from opening the breathing system to four stages of recovery were recorded and, on the day after operation, four questions were used to determine the patient's memory and opinion of the anaesthetic (see below).

Monitoring additional to that required for the above was carried out, but all results for the critical variable, partial pressure of the anaesthetic, were concealed from the anaesthetist until the end of the study. End-tidal partial pressure was used as the best, ethically acceptable estimate of arterial partial pressure. In particular, the value just before each injection was used because, first, that is the moment within each dose interval when, according to the theory,[2] arterial partial pressure should be at the specified level, and second, it was also the moment when there was a minimum in the rate of uptake and hence in the arterial to end-tidal partial pressure difference.

All anaesthetics were given by one anaesthetist (J. M. C. da S.) in a standard manner, with no supplementary drugs likely to affect MAC or arterial pressure; all ward visits were to be made by that anaesthetist.

If there were any deviations from the study design or any fault in the apparatus or recordings, the results for that patient were excluded from analysis and the name of the corresponding volatile anaesthetic returned to the randomization pool.

MEASUREMENTS AND OBSERVATIONS

For control of depth of anaesthesia

Control of depth of anaesthesia depended primarily on SAP in relation to a "reference" preoperative value. Therefore, first, SAP was measured three times, at intervals, during the preoperative visit and twice in the anaesthesia room. The mean of the two lowest of these five measurements was taken as the "reference" SAP. Second, the same non-invasive arterial pressure monitor (UA731 Auto-inflation-Takeda Medical Inc.) was used on the ward and in the anaesthesia room in all patients; a different monitor (Hewlett Packard No. 78352) was used in theatre on all patients, but the two instruments were used on opposite arms of several patients in the anaesthesia room to check that they gave consistent readings. In theatre, arterial pressure was measured immediately before each injection of liquid anaesthetic and 3 min after those from 4 min onwards.

Both instruments also indicated heart rate which was noted each time arterial pressure was measured. Reference heart rate was taken as the mean of the three ward measurements. Sweating and tears were noted as present or absent just before each injection. Any tears were then dried.

For answering the questions posed

A Normac Anaesthetic Agent Monitor (AA-102 Datex Instrumentarium, Helsinki, Finland) was used for measuring anaesthetic partial pressure throughout anaesthesia. It drew a sample flow of approximately 200 ml min^{-1} from a side arm on the patient Y-connector and returned it to the expiratory limb of the closed breathing system. The Normac was calibrated before and after each case, using the calibration canisters supplied by the manufacturer; zero was checked occasionally during each case by briefly sampling room air. End-tidal partial pressure just before each injection of anaesthetic was measured from the chart output, correcting for any slight sensitivity change or zero drift. This gave readings as percentage of ambient atmospheric pressure; therefore barometric pressure was measured to correct to percentage of a standard atmosphere. (This was not done automatically by our Normac.)

Extensive laboratory experiments tested the stability over time of the sensitivity of the measurement system, and the consistency between calibrating mixtures. These showed[10] that drift with time was generally within 2% over 5 h, that the pooled SD between different canisters (on any given day) was 1% of the indicated value and that the sensitivities to the contents of the canisters were within 4% of those of gravimetric mixtures of halothane, enflurane or isoflurane in air, made up in the laboratory.

The four stages of recovery of the patient were those used by Saraiva and colleagues[11]: responds to painful stimulus, obeys commands, answers a simple question, and is fully orientated in time and space.

The four questions used on the day after operation were: (a) What is the last thing you remember before going to sleep? (b) What is the first thing you remember after waking up? (c) Did you have any dreams? (If "yes", what were they?) (d) Would you accept the same type of anaesthetic again?

For supplementary information

A Platon GSYV flowmeter (Platon Flowbits Ltd, Hampshire, UK) (50–500 ml min^{-1}) was placed downstream of the Rotameter of the anaesthesia machine to obtain more accurate and precise measurement of oxygen inflow. A Kontron fuel cell measured continuously oxygen concentration in the inspiratory limb of the breathing system. Body temperature was monitored by an oesophageal probe connected to the Hewlett Packard monitor. The readings of these three monitors were noted just before each injection.

Carboxyhaemoglobin concentration was measured (Ciba-Corning Co-oximeter M2500) in blood samples obtained just before induction and just before opening the breathing system for recovery.

For routine clinical monitoring

Arterial saturation was monitored continuously with a pulse oximeter (Novametrix 515); the Hewlett Packard monitor displayed ECG and heart rate. Also, between the later, widely spaced injections, it automatically measured SAP every 5 min. End-tidal carbon dioxide concentration was monitored by a Datex Normocap instrument, sampling at approximately 100 ml min^{-1} from the catheter mount for only a few breaths just before each injection, without returning the sample to the breathing system.

PROCEDURE

The circle breathing system

The system had an internal volume of 8 litre. It comprised a jumbo soda-lime canister, 2-litre rubber reservoir bag at the end of 1-m length of rubber corrugated tubing, Y-piece and two 1-m corrugated rubber tubes in each limb. The tube at the anaesthetic-machine end of the expiratory limb had a thickened wall at each end. A 25-gauge needle, mounted on an empty 2-ml glass syringe, penetrated the thickened wall at the machine end. For each injection, the empty syringe was replaced by an appropriately loaded syringe and its contents injected.

No more than two patients were studied on any one day. To reduce cross contamination of anaesthetics, two sets of tubing and reservoir bag were maintained and flushed with oxygen overnight after use. The soda-lime canister was flushed with oxygen 6 litre min^{-1} overnight before use and the soda-lime was changed before the second patient in one day. Laboratory experiments[10] showed that with these precautions, cross contamination was always less than 0.05% of an atmosphere.

Apart from the two sets of tubing and bag, the same apparatus was used for all 60 patients with meticulous attention to the sealing of potential leaks and a routine pressure test before each anaesthetic. In the 30 min before induction of anaesthesia, a sequence of operations[10] left the breathing system filled with 55–65% oxygen in nitrogen and ready for an almost loss-free connection to the patient.

Anaesthesia

Patients were premedicated with temazepam 10–30 mg (according to body mass), 1 h before operation. Anaesthesia was induced in the operating theatre with etomidate 0.4 mg kg^{-1} i.v. One-third of the dose was given first, followed by suxamethonium 1 mg kg^{-1} i.v. The patient's lungs were ventilated manually by mask for 1 min, using a Bain breathing system with a fresh-gas flow of oxygen 6 litre min^{-1}; the remainder of the etomidate was then given. After a further 15 s the patient's trachea was intubated with a cuffed tube, the cuff was inflated, breath sounds were checked and the patient was connected to the circle breathing system. Oxygen inflow was set to the estimated metabolic consumption, and the preset 0-min and 1-min doses were injected as described above.

Thereafter, for a "normal" desired depth of anaesthesia, if SAP just before any dose was due was within 20% of the reference SAP, the general rule was that the previous dose of liquid anaesthetic should be repeated; if SAP was more than 20% greater than the reference, a suitably larger dose was given; if more than 20% below, a smaller dose. This rule was ignored if other signs (increasing heart rate, sweating, tears or, very seldom, extrasystoles) suggested that a larger dose was needed. If a dose was due shortly before the anticipated end of surgery, the required depth was recorded as "light" and the dose was omitted or a small dose given. All doses were recorded.

Manual ventilation was used throughout anaesthesia, with neuromuscular block maintained with vecuronium: a dose of 0.1 mg kg^{-1} i.v. was given as soon as the effects of suxamethonium began to wear off, followed by additional smaller doses as required. In accordance with local routine practice, crystalloid and sometimes colloid solutions were administered generously, but blood was given only when the estimated blood loss exceeded 20% of the estimated blood volume. Oxygen inflow was adjusted to maintain the volume of the reservoir bag.

At the end of surgery, neuromuscular block was antagonized with neostigmine 2.5 mg and atropine 1.2 mg i.v. and oxygen inflow was increased to 6 litre min^{-1}. When breathing was adequate, the patient was taken to the recovery room breathing oxygen-enriched air from a Hudson mask. Recovery was followed by the anaesthetist, noting the times from opening of the breathing system to each of the four defined stages. The patient was then returned to the ward.

Blinding

For each patient, the anaesthetist was provided with one of a set of identical dark bottles, containing the appropriate liquid anaesthetic, and a sealed opaque envelope containing the name of the anaesthetic. Both were marked only with the serial number of the patient. After the Normac analyser had been calibrated, an assistant opened the envelope, depressed the appropriate selector button on the analyser and concealed the face of the analyser and the chart record from the anaesthetist throughout the case. To avoid identification of the anaesthetic by smell, the anaesthetist put a few drops of peppermint oil on his surgical mask before opening the numbered bottle of anaesthetic. At the end of the anaesthetic, the assistant rolled up the chart record, sealed it for later analysis and selected enflurane on the analyser so that the anaesthetist could perform the final calibration, still blind. The anaesthetist also wrote down his surmise as to which anaesthetic he had been using. Finally, the assistant marked the anaesthetic on the anaesthetic record card.

DATA PROCESSING AND STATISTICAL ANALYSIS

As a reference level for measured end-tidal partial pressures of the anaesthetics, MAC (as a percentage of a standard atmosphere) was calculated from:

$$\mathrm{MAC}=a\times 10^{bx} \qquad (1)$$

where x=difference in age in years from 40, $b=-0.00269$ and a=MAC at age 40 (0.75%, 1.63% and 1.17% for halothane, enflurane and isoflurane respectively).[12]

As a reference for the actual doses used, the theoretical unit dose, D, for 1.3 MAC was calculated from[2]:

$$D=1.3\times(\mathrm{MAC}/100)\times 2\lambda Q/r \qquad (2)$$

where λ=blood–gas partition coefficient (2.4, 1.9, 1.4 respectively[13]); Q=cardiac output in litre min^{-1}, estimated from $0.2\times M^{3/4}$,[2] where M=body mass in kg and r=ratio of vapour volume at 37 °C to liquid volume (240, 210, 206 respectively[2]). This leads to unit doses of 0.94, 1.86 and 1.00 ml for a 70-kg patient aged 40 yr. Strictly, the dose at 0 min, the "priming" dose, should be calculated differently,[2] but the result is usually very similar so the distinction was ignored as is customary among practitioners of the method.

Comparisons between the three agents were generally by one-way analysis of variance (ANOVA), preceded by a log transform for some variables to make the distribution more nearly normal. Where the ANOVA showed a significant difference between anaesthetic agents, comments on individual agents are generally made only when the 95% confidence intervals of an estimate exclude some expected value. For the irredeemably non-normally distributed volumes of infusion fluid, the Kruskal–Wallis test was used. The chi-square test was used for counts.

Where required, trends of measurements with time were assessed as recommended by Matthews and colleagues[14]: first a straight line or a parabola was fitted to the results for each patient, then simple statistics were performed on the resulting sets of coefficients (intercept, slope, and curvature), weighting each coefficient in inverse proportion to its variance, as provided by the GLIM package[15 16] used for the trend analysis and ANOVA.

Results

Ninety patients were studied because the results from 30 were discarded for a total of 33 reasons: deviations from study design (eight), faults in the recordings (14), leaks from the breathing system (five) and duration of anaesthesia less than 75 min (six).

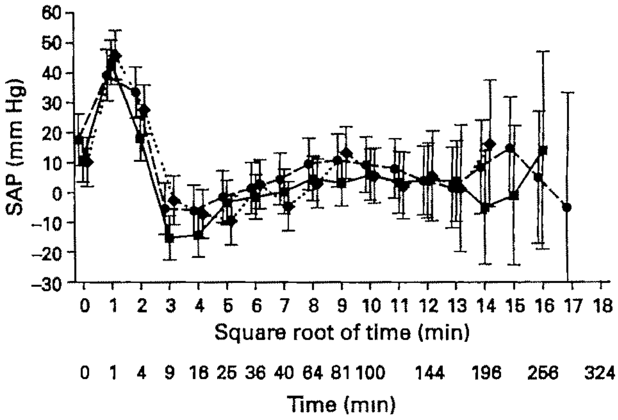

Figure 1 Mean and 95% confidence intervals of systolic arterial pressure (SAP) before each injection (as a difference from the reference SAP), against the square root of time, for the three anaesthetics. The positive drift from 9 min onwards is adequately described by a common slope of 1.9 (SEM 0.28) mm Hg per dose interval ($P<0.001$). At the later times the means become erratic and the confidence limits wider because the number of patients still anaesthetized becomes progressively fewer. Data for enflurane (●) and isoflurane (◆) have been slightly time-shifted relative to halothane (■) to clarify the display.

Table 1 Patient data. s=Superficial, u=upper abdominal, l=lower abdominal

	Sex (M/F)	ASA grade (I/II)	Age (yr)	Weight (kg)	Height (m)	Surgery (s/u/l)	Duration of anaesthesia (min)
Halothane							
n	6/14	13/7				10/4/6	
Mean			43.6	69.9	1.65		137.4
Range			21–65	43–95	1.51–1.85		79–258
Enflurane							
n	6/14	11/9				6/7/7	
Mean			45.4	68.0	1.63		169.1
Range			25–63	50–104	1.43–1.85		79–306
Isoflurane							
n	10/10	13/7				5/9/6	
Mean			45.4	63.5	1.66		130.3
Range			20–65	48–82	1.50–1.80		76–210

The three groups of patients were similar in most respects but mean duration of anaesthesia was greater in the enflurane group (table 1).

PREOPERATIVE RESULTS

The doses of etomidate and suxamethonium were fixed on a mg kg^{-1} basis. For the other preoperative variables, the ranges of mean values for the three groups of patients were: temazepam dose 0.323–0.325 mg kg^{-1}, reference SAP 127–128 mm Hg and reference heart rate 79–82 beat min^{-1}.

PEROPERATIVE RESULTS

Haemodynamic variables

SAP increased sharply initially but from 9 min onwards it was, on average, close to the reference SAP for all three anaesthetic agents with a slow but significant ($P<0.001$) positive drift of 1.7 mm Hg per dose interval, from a little less than the reference SAP to a little more (fig. 1). From 9 min onwards, 86% of individual measurements were within 20% of the reference SAP. This was true both immediately before, and 3 min after, each injection, with a mean decrease of 3–4 mm Hg in that 3 min. Differences between agents were small (<1 mm Hg) and non-significant.

Mean heart rate (before injection) from 9 min onwards was significantly greater than the reference heart rate for enflurane and isoflurane (by 11 and 17 beat min^{-1}, respectively). With each injection there was a mean decrease of 4 beat min^{-1} with halothane.

Clinical signs

Sweating was never observed during the study; tears were recorded only at 1 or 4 min, for six, nine and four patients in the halothane, enflurane and isoflurane groups, respectively. The differences were not significant.

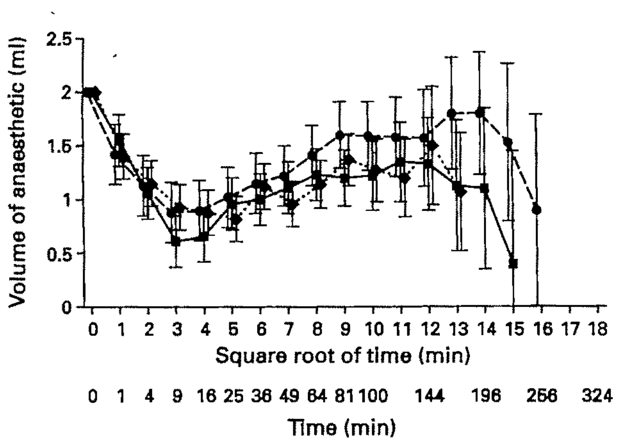

Figure 2 Mean and 95% confidence intervals of the volumes of injected liquid anaesthetic, against the square root of time, for the three anaesthetics. The final volume was omitted from the calculations when the required depth of anaesthesia at that time was recorded as "light". The positive drift from 9 min onwards is adequately described by a common slope of 0.066 (SEM 0.013) ml per dose interval ($P<0.001$). Data for enflurane (●) and isoflurane (◆) have been slightly time-shifted relative to halothane (■) to clarify the display.

Table 2 Mean volume of liquid anaesthetic injected at each dose (excluding the last if the required depth at that time was "light"): actual, predicted (equation 1) and ratio, and also revised predicted (see discussion) and ratio. Calculated as follows: for each patient, mean of all measurements; for each anaesthetic, mean and SD of these patient means and 95% confidence interval (CI) of the resulting mean. Therefore, SD refers to variation between patients. P=Probability (by one-way analysis of variance) that the differences between anaesthetics are caused by chance. [a]Predicted from equation (2) for 1.3 MAC. [b]Predicted for mean actual pre-injection end-tidal partial pressure (table 3)

	Mean	SD	95%CI	P
Actual volume (ml)				
Halothane	1.144	0.354	0.98–1.31	
Enflurane	1.316	0.399	1.13–1.50	ns
Isoflurane	1.176	0.280	1.04–1.31	
Predicted volume[a] (ml)				
Halothane	0.921	0.174	0.84–1.00	
Enflurane	1.761	0.369	1.59–1.93	—
Isoflurane	0.901	0.124	0.85–0.96	
Ratio (actual/predicted)				
Halothane	1.237	0.293	1.10–1.37	
Enflurane	0.752	0.184	0.67–0.84	<0.001
Isoflurane	1.327	0.366	1.16–1.50	
Revised predicted[b] volume (ml)				
Halothane	0.743	0.354	0.58–0.91	
Enflurane	0.586	0.158	0.51–0.66	0.03
Isoflurane	0.550	0.157	0.48–0.62	
Ratio (actual/revised-predicted)				
Halothane	1.709	0.547	1.45–1.96	
Enflurane	2.315	0.638	2.02–2.61	0.001
Isoflurane	2.190	0.353	2.03–2.36	

Cardiovascular complications (SAP less than 60% of the reference value, heart rate less than 50 beat min^{-1} or greater than 120 beat min^{-1}, AV junctional rhythm or arrhythmia, or a combination of these) occurred at some time during anaesthesia in 14 patients with halothane, four with enflurane and eight with isoflurane—an overall incidence of 43%. The differences were significant ($P<0.01$).

Anaesthetic variables

Mean volumes of liquid anaesthetic injected showed some systematic variation with time (fig. 2) but were similar for all three agents despite the differences in predicted unit dose. Therefore, for each patient, the following values were calculated: predicted dose, mean actual dose (omitting the last one if the required depth at that time was recorded as "light") and the ratio of the two. These were then averaged for each agent. This showed (upper part of table 2) that the mean enflurane dose was 25% less than that predicted and the mean halothane and isoflurane doses were 24% and 33% more, respectively ($P<0.001$).

The type of surgery had no significant effect on the amount of anaesthetic required, either in terms of absolute dose ($P=0.7$) or relative to the predicted dose ($P=0.5$).

In all patients the anaesthetic partial pressure showed a sawtooth pattern in end-inspired and end-tidal values and in the amplitude of the difference between them (fig. 3): all three aspects increased rapidly after each dose, reached a peak in approximately 3 min and then decreased slowly until the next dose.

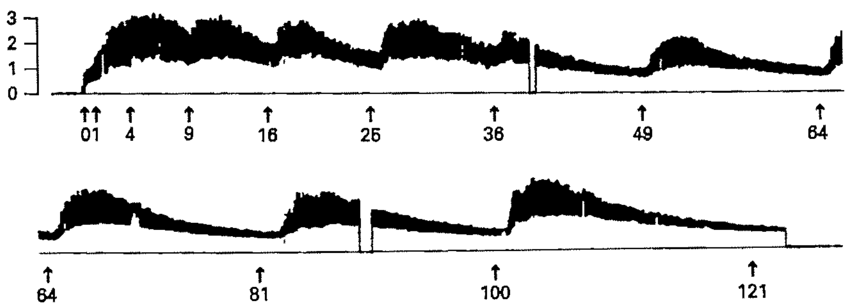

Figure 3 Sample recording of anaesthetic concentration against time. The background grid has been suppressed; a calibration scale (% atmosphere enflurane in this example) and a zero line have been added. Arrows indicate the time in minutes at which each injection was due. Note the sawtooth pattern in inspired (upper limit of trace) and end-tidal (lower limit) concentrations produced by periodic injections of liquid anaesthetic at the times indicated. Note also the occasional zero checks and that no injection was made at 121 min.

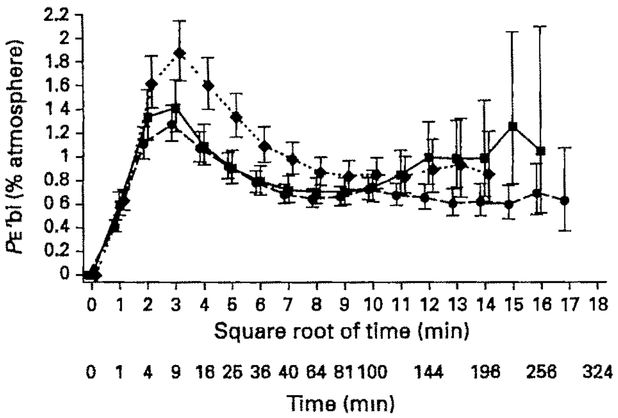

Figure 4 Mean and 95% confidence intervals of pre-injection end-tidal partial pressure (*P*E'bi) against the square root of time, for the three anaesthetics. The apparent positive drift for halothane after 49 min was not significant (P=0.5) and arose partly because some of those patients who underwent prolonged halothane anaesthesia had consistently large values of *P*E'bi throughout anaesthesia. Data for enflurane (●) and isoflurane (◆) have been slightly time-shifted relative to halothane (■) to clarify the display.

End-tidal partial pressure just before each injection (*P*E'bi) was not constant: the means for each agent (fig. 4) increased to a peak at 4–9 min and stabilized at a steady level from 49 min onwards. The apparent positive drift with halothane at the later times was not significant (P=0.5) and was partly because some of those patients who underwent prolonged anaesthesia with halothane had consistently large values of *P*E'bi throughout anaesthesia.

Table 3 Geometric mean pre-injection end-tidal partial pressures of anaesthetics (averaged from 49 min onwards). Calculated as follows: (a) logs of all measurements; (b) for each patient, mean of all logs; (c) for each anaesthetic, mean and SD of these log means, that is variation between patients, and 95% confidence interval (CI) of the resulting mean for each anaesthetic; and (d) convert means and CI (but not SD) back to linear values. P=Probability (by one-way analysis of variance) that the differences between anaesthetics are caused by chance. *Corrected for age according to equation (1)

	Geometric mean	SD of logs	95%CI	P
Pre-injection end-tidal partial pressure (% std atmosphere)				
Halothane	0.709	0.182	0.58–0.86	0.048
Enflurane	0.670	0.118	0.59–0.76	
Isoflurane	0.870	0.141	0.75–1.01	
Pre-injection end-tidal partial pressure (MAC* units)				
Halothane	0.967	0.168	0.81–1.16	<0.001
Enflurane	0.425	0.109	0.38–0.48	
Isoflurane	0.769	0.137	0.66–0.89	

Steady-state partial pressures were summarized by averaging, for each patient, all *P*E'bi values from 49 min onwards, calculating means of these averages for each anaesthetic and also expressing them in MAC units, corrected for age (table 3). The differences between anaesthetics in terms of actual partial pressure were small but, in terms of MAC units, the differences were large (approximately 1, 0.5 and 0.75 MAC for halothane, enflurane and isoflurane, respectively) and highly significant (P<0.001).

Other variables

Mean rates of vecuronium use were 1.4–1.5 μg kg^{-1} min^{-1} for the three groups. Hartmann's solution was used in all patients, colloids in approximately 50% and packed red cells in less than 25%. Mean total fluid use ranged from 13 ml kg^{-1} h^{-1} for isoflurane to 16 ml kg^{-1} h^{-1} for halothane. There were no significant differences between anaesthetics in any of these features.

From 9 min onwards overall mean oxygen inflow required to maintain the volume of the breathing system was 212 ml min^{-1} (STPD) with negligible drift and no significant differences between anaesthetics. Allowing for an estimated oxygen leakage of 36 ml min^{-1} (see discussion below) this gives an oxygen consumption of 176 ml min^{-1}, close to the 179 ml min^{-1} predicted by Nunn[17] for our average patient (table 1).

Inspired oxygen concentration was similar for the three agents and averaged 58% overall with all instantaneous values between 42% and 88%.

Overall mean end-tidal $P\text{CO}_2$ was 5.0 kPa and overall mean arterial saturation by pulse oximetry was 99%; there were very small differences (<1%) between groups. The lowest recorded saturation was 95%. All but three individual values of end-tidal $P\text{CO}_2$ were between 4.0 and 5.9 kPa.

Oesophageal temperature decreased from an overall mean of 36.3 °C to 35.8 °C at 64 min.

Overall mean carboxyhaemoglobin concentration changed from 2.8% before operation to 3.0% at the end of anaesthesia, with 95% confidence limits for the mean change of −0.1 to +0.4%.

Table 4 Recovery times (min). Analysis performed on log time. *P*=Probability (by one-way analysis of variance) that the differences between anaesthetics are caused by chance

	Geometric mean	SD of logs	95%CI	*P*
Stage 1: patient responds to painful stimulus				
Halothane	2.1	0.304	1.5–2.9	
Enflurane	1.5	0.182	1.2–1.8	0.01
Isoflurane	3.0	0.411	1.9–4.7	
Stage 2: patient obeys command				
Halothane	7.1	0.281	5.2–9.6	
Enflurane	4.1	0.190	3.3–5.0	0.001
Isoflurane	8.8	0.331	6.2–12.5	
Stage 3: patient answers a simple question				
Halothane	12.3	0.272	9.2–16.5	
Enflurane	7.4	0.212	5.9–9.3	0.001
Isoflurane	15.0	0.278	11.1–20.3	
Stage 4: patient is fully orientated in time and space				
Halothane	17.5	0.243	13.5–22.7	
Enflurane	10.8	0 224	8.5–13.7	0.002
Isoflurane	20.3	0.263	15.3–26.9	

Table 5 Responses to the question "What is the last thing you remember before going to sleep?" *P*=Probability (by chi-square test) that the difference between anaesthetics is caused by chance. *"I am going to put you to sleep"

	Premedication	Being in theatre	Information*	Pain of etomidate injection	*P*
Halothane	5	2	9	4	
Enflurane	0	4	13	3	0.14
Isoflurane	3	7	8	2	

Table 6 Success rate in identifying the anaesthetic used. The chance success rate for each cell is 6.7, with 95% confidence limits of 2.5 and 10.8. Overall probability that success rate is caused by chance (by chi-square test): *P*<0.001

Anaesthetist's opinion	Agent actually used			Total
	Halothane	Enflurane	Isoflurane	
Halothane	16	2	5	23
Enflurane	2	6	9	17
Isoflurane	2	12	6	20
Total	20	20	20	60

POSTOPERATIVE RESULTS

In the enflurane group all four stages of recovery were reached in approximately half the time taken in the isoflurane group; the times for the halothane group were intermediate (table 4). Differences between groups were significant.

On the day after operation, memory of the later preoperative events was more frequent in patients in the enflurane group than in the two other groups (table 5) but the differences were not significant (*P*=0.14). In all three groups, six patients remembered the recovery room; 14 remembered nothing before their return to the ward. No patient reported dreams and all said that they would accept the same type of anaesthetic again.

The anaesthetist was generally able to identify the use of halothane, but scored only in accordance with chance in correctly identifying enflurane and isoflurane (table 6).

Discussion

THE FOUR QUESTIONS

Are the doses and end-tidal partial pressures consistent with Lowe's theory?

The theory is that, if the predicted dose is given at the specified times, arterial partial pressure increases rapidly to the specified level and then remains constant, but there needs to be "procedural modifications according to patient response".[2] In this study the specified level was 1.3 MAC, the doses were given at the specified times, but the sizes of the doses, after the first two, were chosen primarily on the basis of maintaining normal SAP.

Anomalies of dosage. Although all mean actual doses for each anaesthetic were within 33% of predicted (upper part of table 2), steady state values (49 min onwards) of *P*E'bi were much less than 1.3 MAC (table 3). Accordingly, the predicted doses for these actual *P*E'bi were much smaller and the actual doses were about twice these revised predicted doses (lower part of table 2).

This excess of actual dosage over predicted dosage corresponded to an average excess rate of usage of anaesthetic of approximately 11 ml of vapour per minute. An alternative estimate of excess usage of anaesthetic was obtained from the positive drift of dosage with time (fig. 2) which corresponded to a steady loss of 7 ml of vapour per min.

Several factors could contribute to the apparent need for this excess of 7–11 ml of vapour per min: diffusion into and through the walls of the breathing system; loss in gas leaking from the system; direct uptake into fat from adjacent tissues[18]; metabolism, particularly of halothane[19]; and the fact that, during the period of interest (9–121 min), the theoretical[3] rate of uptake declines a little more slowly than in accordance with the square root of time. Quantitative estimates of these factors (based on laboratory experiments for absorption into the walls of the breathing system) were sufficient to account for a total of 9 ml of vapour per min. Although loss through the skin would be negligible,[20] there may have been appreciable loss through the operation wound, especially in those patients undergoing abdominal surgery.[21] Similar excesses of uptake over that predicted from the square-root-of-time theory have been reported by others for continuous-inflow versions of the Lowe method.[22]

Anomalies of end-tidal partial pressure. The clinical aim was to maintain SAP close to the reference level. Therefore, it is not surprising that *P*E'bi showed an initial "overpressure" before reaching a steady level (fig. 4). However, as SAP returned to the reference level within 9 min (fig. 1), it is at first surprising that the *P*E'bi overpressure lasted until 49 min (fig. 4). However, close inspection of figure 1 reveals that, after the initial hypertension, SAP showed a trough at 9–16 min and then drifted back up above the reference level. As SAP was in part inversely dependent on end-tidal partial pressure, this upward drift in SAP can explain some of the decline in *P*E'bi.

Can the findings of Couto da Silva[5–8] be replicated in a double-blind study?

The findings that the doses of enflurane required were less than predicted, and that recovery from enflurane was more rapid than that from halothane or isoflurane were confirmed (tables 2, 4) and the study was mostly blind: although the anaesthetist usually identified halothane (table 6), it generally took approximately 25 min to form a firm opinion so that the first five or six injections of halothane (half the average total number) were made blind, as were all injections of enflurane and isoflurane.

Can the cause of the discrepancy between agents be elucidated?

Compared with halothane and isoflurane, enflurane required approximately 50% of the dose (as a fraction of predicted) (upper part of table 2), and produced approximately half the steady-state *P*E'bi (in MAC units) (table 3). Therefore, either the MAC of enflurane is less than previously believed or patients who received enflurane were more lightly anaesthetized.

The time taken to reach each of the four stages of recovery was only approximately 50% as long with enflurane as with halothane or isoflurane (table 4), and memories of preoperative events were greater with enflurane, although this was not significant (table 5). Therefore, it must be concluded that patients receiving enflurane were less deeply anaesthetized. As administration of all agents was based mainly on maintenance of the reference SAP, it must also be concluded that, at any given MAC level, enflurane is a more potent hypotensive agent than halothane or isoflurane. These conclusions are supported by other studies in different circumstances.[23–27]

Does the Lowe technique produce satisfactory anaesthesia?

Despite the inevitable sawtooth pattern of end-tidal partial pressure (fig. 3), SAP decreased by only 3–4 mm Hg, on average, as a result of each injection. Also, after an initial hypertension (fig. 1), 86% of all measurements were within the target range (reference SAP ±20%).

The overall incidence of cardiac rhythm disturbances (43%) was less than the "60% or more" quoted by Atlee[28] as common, although marginally greater (70%) with halothane. However, these disturbances generally appeared as a new dose became due (and partial pressure was at a minimum) and disappeared soon afterwards.

Mean steady-state *P*E'bi was less than the MAC for all three anaesthetics (table 3) (less than 50% of the MAC for enflurane) and the four stages of recovery were reached in times that were very short (table 4) compared with those reported for recovery to the same four stages from halothane and nitrous oxide anaesthesia.[11] However, no patient admitted to any dreams and all were prepared to have the same type of anaesthetic again.

We conclude that anaesthesia was indeed satisfactory although we suggest some improvements below.

LIMITATIONS OF THE PRESENT STUDY

Errors in the measurement of anaesthetic partial pressure

The Normac, in common with some other multi-gas monitors, measures all volatile anaesthetics by infrared absorption at 3.3 μm. Therefore, interference from "foreign" gases and vapours is possible, particularly with a closed system in which such gases may accumulate, and especially when measuring halothane for which the analyser gain is set approximately five times greater than for enflurane or isoflurane. Generally, this does not appear to be a serious problem but two recent studies from Belgium[29 30] have shown methane accumulating at approximately 700 ppm per hour leading to apparent halothane concentrations (measured at 3.3 μm) increasing by approximately 0.7% per hour.

In this study, halothane was unique in showing a positive drift in partial pressure (after 49 min) but the drift was not significant (0.04% per hour) and so of negligible importance. As methane is produced by microbial fermentation of carbohydrates, mainly in the distal colon,[30] the difference from patients in Belgium may perhaps be related to a difference in gut flora or diet.

Differences between end-tidal and arterial partial pressure

Lowe's theory is based on arterial partial pressures; we measured end-tidal partial pressures. The former must have been less than the latter throughout our study because of continuing uptake: even just before the last dose, inspired partial pressure was always a little greater than end-tidal. However, virtually all MAC values are based[12] on measurements of end-tidal partial pressure. Therefore, our *P*E'bi values expressed in MAC units should be consistent with those in other studies.

Leakage rate

The outflow from the Normac analyser includes a small flow of air (30 ml min^{-1} in our analyser) drawn in as a reference gas. The nitrogen content of this air (24 ml min^{-1}) forms a convenient tracer gas from which leakage can be calculated. First, after approximately 2 h, oxygen concentration in the breathing system reached a plateau (60% on average). Therefore, at that time, the inflow of nitrogen must have equalled the outflow, and nitrogen excretion from the body would by then be negligible. Accordingly, the 24 ml min^{-1} from the Normac formed 40% of the leakage rate. Therefore, total leakage was approximately 60 ml min^{-1} and included approximately 36 ml min^{-1} of oxygen.

LIMITATIONS AND IMPROVEMENTS OF THIS METHOD OF ANAESTHESIA

Although 30 of 90 patients were excluded, in only six instances were the causes relevant to clinical use of the technique: five of these were leaks (only one of which led to abandonment of the closed system) and one was use of adrenaline by the surgeon which interfered with judgement of depth of anaesthesia. Therefore, the technique is widely applicable.

The instance of adrenaline use draws attention to a general problem in using arterial pressure as a main measure of depth of anaesthesia: any drug, or other event, that has a direct effect on arterial pressure but not on depth of anaesthesia must be avoided, or allowed for, or another method of assessing depth must be used.

In routine clinical practice, anaesthesia could be deepened rapidly or lightened at any time by an extra injection or by opening the system, or even by inserting a charcoal absorber.[31] However, the need did not arise in any of the 90 patients entered into this study.

We used a short-acting non-analgesic induction agent (etomidate) and no opioid, to ensure minimum interference with comparison of the volatile agents. Therefore, in routine clinical practice, the initial hypertension could be reduced by using more appropriate drugs and reducing the early doses of liquid anaesthetic correspondingly.

An enflurane PE'bi value of 0.42 MAC obviously raises concerns about awareness, even though MAC-awake (the concentration at which the patient just responds to command) has been reported to be 0.27 MAC for enflurane.[32] In this respect, it is important to note that the zero incidence of awareness found in our 20 patients implies that the upper 95% confidence limit, for the incidence in a population anaesthetized in the same way, would be three in 20 (15%).[33] Accordingly, if enflurane is to be used with this technique, it may be advisable to aim for an SAP which is less than the reference value.

Age- and sex-standardized tables of SAP[34] have been used[35] as a basis for a reference SAP, but the differences of our reference SAP values from those derived from these tables had a mean of −3.4 mm Hg and an SD of 14 mm Hg. Therefore, the effort of taking the time to obtain a valid reference SAP for each patient may be repaid.

A common concern with closed-system anaesthesia is that carbon monoxide may accumulate. A recent study[36] showed that this arose from degradation of several volatile anaesthetics by the carbon dioxide absorbent, especially when this was dry. However, although we flushed the soda lime with 6 litre min^{-1} of oxygen overnight, blood carboxyhaemoglobin increased on average only by 0.2% (ns) with an upper confidence limit of 0.4% and an SD of 0.8%.

RECOMMENDATIONS

The Lowe intermittent-injection square-root-of-time method of closed-system anaesthesia provides the basis of a simple, economic method of anaesthesia. The calculated unit dose can be used as a guide, but the choice of individual doses in each patient must depend on the skill of the anaesthetist in assessing depth of anaesthesia. If this assessment is based mainly on maintaining a normal SAP, the resulting end-tidal partial pressures are likely to be much less than 1.3 MAC, especially for enflurane, where it may be advisable to aim for perhaps 10% less than the preoperative value.

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REVIEW ARTICLE

Thorascopic sympathectomy in the treatment of palmar hyperhidrosis: anaesthetic implications

B. FREDMAN, D. OLSFANGER AND R. JEDEIKIN

As a result of technical advances, endoscopic surgery has become the technique of choice for many intra-abdominal and thoracic surgical procedures. The advantages of endoscopic surgery include less postoperative pain, shorter hospital admission, earlier return to normal activity and improved cosmetic result.[15 17 19 54]

Thorascopic surgery differs from other endoscopic procedures in that adequate surgical exposure requires collapse or retraction of the operative lung. Whether achieved by one-lung ventilation or carbon dioxide insufflation, these interventions may be associated with significant cardiorespiratory disturbances.

In this review thorascopic sympathectomy in the treatment of palmar hyperhidrosis and related controversies are discussed. Special emphasis is placed on the anaesthetic considerations of this procedure. Finally, based on our clinical experience, recommendations are made regarding the anaesthetic of choice.

Palmar hyperhidrosis

Primary palmar hyperhidrosis (sweating that exceeds that needed for thermoregulation) is a rare condition of unknown aetiology which has an estimated incidence of 0.6–1.0%.[1] Occurring mostly in otherwise healthy adolescents, this condition is usually bilateral, characterized by excessive sweating, often affecting the palms of the hands, axillae and feet. While moist axillae and feet cause considerable discomfort, wet or dripping hands result in serious functional disability with consequent social and psychological handicaps.[44]

Drug therapy,[50] biofeedback,[20] iontophoresis[34] and percutaneous phenol block[16] have been attempted. However, medical treatment of palmar hyperhidrosis appears to be successful only in the mildest of cases.[11] In contrast, surgical ablation of the upper thoracic sympathetic chain is associated with excellent results. Therefore, in view of the poor results associated with medical therapy, surgical intervention has become the treatment of choice in the primary management of hyperhidrosis.[10 14 32 38]

Surgical approach: open *vs* thorascopic

As the upper thoracic sympathetic chain is relatively inaccessible, open surgical sympathectomy was traditionally performed. This was done usually via the supraclavicular,[53] axillary[5] or posterior approach.[3] However, none of these procedures is simple and all carry some risk of complications. In a retrospective study of 475 patients who underwent open supraclavicular sympathectomy, early postoperative complications included transient Horner's syndrome (12%), pneumothorax (6%) and pleural effusion (4%). Compensatory sweating (80%), gustatory phenomena (75%), phantom sweating (53%), respiratory discomfort (22%) and wound pain (12%) occurred as late postoperative sequelae.[1] Because of these early and delayed complications, surgeons have been reluctant to perform open sympathectomy when treating a non-life threatening condition such as hyperhidrosis.

The introduction of thorascopic electrocauterization of the sympathetic chain by Kux[32] has significantly simplified the procedure and resulted in an increased interest in both palmar hyperhidrosis and its surgical treatment. Gothberg, Drott and Claes[23] reported excellent results after 1274 thorascopic sympathectomies in 602 patients. The procedure was successful in 99% of patients with delayed recurrence of symptoms occurring in 0.8% of cases. One case of Horner's syndrome was reported. The incidence of pneumothorax and haemothorax were 0.4% and 0.15%, respectively. Furthermore, patient-generated visual analogue pain scores demonstrated minimal postoperative pain.[23] We speculate that the high complication rate (Horner's syndrome, pneumothorax, pleural effusion) associated with open sympathectomy is the result of local tissue damage during surgical dissection. Specifically, supraclavicular dissection may result in inadvertent trauma to the stellate ganglion with consequent transient or permanent

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Key words
Surgery, thoracic. Surgery, endoscopy. Complications, palmar hyperhidrosis.

BRIAN FREDMAN, MB, BCH, DAVID OLSFANGER, MB, CHB, ROBERT JEDEIKIN*, BSC, MB CHB, FFA(SA), Department of Anesthesiology and Critical Care, Meir Hospital, Kfar Sava, The Sackler School of Medicine, Tel Aviv University, Tel Aviv, Israel.

*Address for correspondence: Department of Anesthesiology and Critical Care, Meir Hospital, Kfar Sava 44281, Israel

Horner's syndrome.[1] In contrast, during thorascopic sympathectomy the surgical field is easily seen with little associated tissue trauma.

Unfortunately, there are few randomized, prospective studies comparing overall patient outcome and complication rates between the two surgical procedures. In a prospective, randomized study of 24 patients allocated to undergo either bilateral open supraclavicular thoracic sympathectomy or bilateral thorascopic sympathectomy, Hashmonai, Kopelman and Schein demonstrated prolonged postoperative pain in the thorascopic group. However, no other differences were found between the two treatment modalities.[27] The differences between these findings and those of Gothberg, Drott and Claes[23] may be a result of the length of the surgical procedure (157 min *vs* 25 min). However, the exact mechanism of this pain is unclear. Our clinical experience correlates with the minimal postoperative pain reported by Gothberg, Drott and Claes.[23]

Both open and thorascopic sympathectomy may be complicated by postoperative compensatory hyperhidrosis of the torso, buttocks and thigh. However, the incidence of this condition after thorascopic sympathectomy requires further investigation. While the exact pathophysiology of this condition is unclear, it has been suggested that compensatory sweating is caused by a centrally mediated abnormality of thermoregulation and sudomotor function.[2 13 49] Compared with the preoperative condition, compensatory hyperhidrosis is usually mild.

Preoperative preparation

Patients should be well counselled and fully understand the procedure, its success rate and the possibility of transient postoperative chest pain and delayed compensatory sweating. As the majority of patients undergoing thorascopic sympathectomy are young and otherwise healthy adolescents, this procedure is ideally suited to "same day" admission. Following recent advances in preoperative evaluation, unless specifically indicated by history and physical examination, no laboratory investigations are necessary.[47]

In our experience the only cost effective preoperative investigation is a baseline chest x-ray. This is useful in the preoperative diagnosis of pulmonary adhesions and when evaluating possible postoperative pulmonary pathology.

Depending on physician and patient preference, either no premedication or a short-acting benzodiazepine should be administered.[43]

Anaesthetic technique

As the thoracic sympathetic chain lies on the posterior chest wall and is hidden by the lung parenchyma, the ipsilateral lung must be either collapsed or retracted to facilitate adequate surgical exposure. This may be performed via endobronchial anaesthesia or by carbon dioxide insufflation in combination with a tracheal tube. Recently, the use of a laryngeal mask airway (LMA) and face mask anaesthesia have also been reported. These fundamental differences in anaesthetic technique make prospective, randomized, double-blind studies difficult to perform.

Irrespective of the anaesthetic technique, unless specifically contraindicated (unilateral symptoms, pulmonary adhesions), bilateral sympathectomy is performed.

ENDOBRONCHIAL ANAESTHESIA

Endobronchial anaesthesia provides excellent surgical conditions and is associated with a low risk of surgically induced injury to the lung, stellate ganglion and major thoracic blood vessels.

Having placed the endobronchial tube the patient's arms are abducted to 90°. Thereafter, the tube is opened to the atmosphere and the ipsilateral lung is collapsed in order to separate the parietal from the visceral pleura. This procedure prevents lung injury when the Verres' needle, trocar and endoscope are inserted. However, confirmation of tube positioning by observation and auscultation is time consuming and not always reliable.[6 51] While fibreoptic laryngoscopy may be performed,[8] this procedure requires sophisticated equipment and its reliability is operator dependent. Incorrect placement of the double-lumen tube may result in failure of the ipsilateral lung to "fall away" with consequent instrument-induced lung injury.

During endobronchial anaesthesia carbon dioxide insufflation augments lung collapse and therefore provides additional lung protection during insertion of the endoscopic instruments. Thereafter, collapse of the entire lung is accomplished and maintained by the endobronchial tube and carbon dioxide insufflation plays no part in facilitating surgical exposure.

ANAESTHESIA USING A TRACHEAL TUBE

Anaesthesia with a tracheal tube has many advantages compared with the endobronchial technique (table 1). The tracheal tube is quickly and easily placed, and requires no special expertise or equipment to confirm correct placement. Furthermore, the tracheal tube is significantly less expensive compared with the endobronchial tube.

Table 1 Advantages and disadvantages of anaesthesia with a tracheal tube compared with the endobronchial technique. PHV=Pulmonary hypoxic vasoconstriction. Because of insufficient data at time of publication the advantages and disadvantages of LMA and face mask anaesthesia have been omitted

Advantages	Disadvantages
Endobronchial technique	
Low incidence of tissue injury	Confirm tube position
No accidental re-expansion	Abolish PHV
Tracheal tube	
Quick, easy tube placement	Possible lung injury
No abolition of PHV	Surgical field insufflator dependent
Improved oxygenation	Transient hypotension following positioning
Less expensive	Possible tension pneumothorax

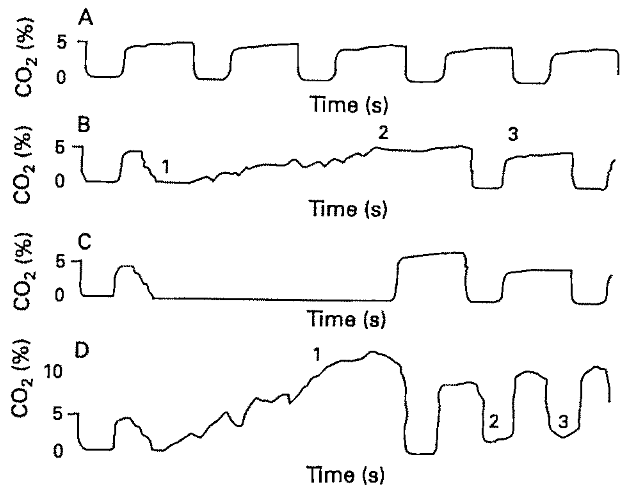

Figure 1 Diagrammatic representation of the capnograph waveform seen during thorascopic sympathectomy with anaesthesia using a tracheal tube. A: Normal, both lungs ventilated. B: Correct placement of the Verres' needle in the intrapleural space is confirmed; ventilation stopped, expiratory valve opened to the atmosphere, expired carbon dioxide concentration decreases to zero (point No. 1); 0.5 litre of carbon dioxide insufflated through the Verres' needle partially collapses the lung and expired carbon dioxide concentration gradually returns to 4–5% (point No. 2); lung ventilation resumed, normal waveform during additional 0.5–1.5 litre of carbon dioxide insufflation (point No. 3). C: Verres' needle in chest wall of pleural adhesions prevents lung collapse; no increase in expired carbon dioxide concentration from zero during insufflation. D: Lung puncture; during insufflation expired concentration of carbon dioxide increases to about 8–12% (point No. 1), on resumption of ventilation end-inspired concentration does not return to zero but increases with each ventilation (point Nos 2 and 3). (Reprinted from *British Journal of Anaesthesia* 1995; 74: 141-144.)

Despite these advantages a clear understanding of the potential pitfalls is essential in order to maintain the operative field and prevent respiratory and haemodynamic complications.

After induction of general anaesthesia, in order to prevent Verres' needle-induced lung injury, immediately before inserting the needle, apnoea is induced and the expiratory valve opened to the atmosphere. The Verres' needle is then inserted into the pleural space via a small incision in the fourth intercostal space, midaxillary line and the lung partially collapsed and compressed by insufflating 0.5 litre of carbon dioxide. The end-tidal carbon dioxide tracing must be interpreted carefully in order to verify placement of the Verres' needle and exclude accidental lung puncture (fig. 1).

In contrast with endobronchial anaesthesia, when using a tracheal tube carbon dioxide is insufflated continuously into the intrapleural space until the end of surgery. This is achieved by using a variable flow carbon dioxide insufflator. The resultant continuous positive intrapleural pressure, together with placement of the patient in the semi-sitting position, provide adequate exposure of the upper thoracic cavity.

A disadvantage of the tracheal tube technique is that when intrapleural pressure decreases, the ipsilateral lung rapidly re-inflates and obstructs the surgical field. This may be produced by cessation of carbon dioxide insufflation, leak from the delivery system or use of excessive intrapleural suction to control bleeding.

LARYNGEAL MASK AIRWAY AND FACE MASK ANAESTHESIA

In a non-English study, the efficacy of a laryngeal mask airway (LMA) was compared with a double-lumen endobronchial tube and arterial oxygen saturation (Sp_{O_2}) was shown to be significantly ($P<0.001$) improved in the LMA group. However, as total lung collapse is associated with ventilation–perfusion ($\dot{V}/\dot{Q}$) mismatch and shunting, it is not surprising that two-lung ventilation via an LMA resulted in improved patient oxygenation.[28]

In a similar study, Lieou and colleagues administered total i.v. anaesthesia with a neuromuscular blocking agent to 198 patients undergoing thorascopic sympathectomy. In all cases the airway was maintained using a tight fitting face mask and ventilation assisted. Throughout the procedure mean Sp_{O_2} and end-tidal carbon dioxide were 99% and 36%, respectively.[35]

While these studies represent a deviation from the traditional practice of intubation and controlled ventilation, language limitations make critical analysis difficult.

Special considerations

HYPOXAEMIA

Hypoxaemia is of major concern during thorascopic sympathectomy. However, the pathophysiology of hypoxaemia and consequent decrease in Sp_{O_2} differs between the two anaesthetic techniques.

Endobronchial intubation

The normal physiological response to massive atelectasis is an increase in pulmonary vascular resistance (hypoxic pulmonary vasoconstriction) with re-routing of blood to well ventilated lung zones and consequent improvement in Pa_{O_2}. However, during endobronchial anaesthesia for thoracic sympathectomy there is apparent failure of this compensatory mechanism. When more than 70% of the lung is atelectatic, compensation by hypoxic pulmonary vasoconstriction appears to be ineffective.[37] Furthermore, in *in vitro*[9] and animal studies,[7] inhalation anaesthetic agents have been shown to depress hypoxic pulmonary vasoconstriction. However, these findings have not been confirmed in clinical studies where 1 MAC of either halothane or isoflurane was administered.[46]

In a study of 101 sympathectomies in 58 patients, despite administration of 100% oxygen, Sp_{O_2} was 99–100% in 32 patients, 95–98% in 21 patients and in three patients an Sp_{O_2} value of less than 95% was recorded.[30] Furthermore, in a study by Hartrey and colleagues, Sp_{O_2} <95% was demonstrated in 74% of cases receiving an FI_{O_2} of 0.5.[26] This $\dot{V}/\dot{Q}$ mismatch and shunt effect was confirmed when arterial blood-gas measurements were made during one-lung ventilation and compared with baseline values during two-lung ventilation. In 25% of sympathectomies studied, Pa_{O_2} <15 kPa was recorded. It should be remembered that after re-inflation of the collapsed lung, $\dot{V}/\dot{Q}$ mismatch may be persistent and that time is required for the lung to recover its full oxygenation capacity.[29 45] This problem period has been managed successfully with high frequency jet ventilation while administering 100% oxygen.[24]

During endobronchial anaesthesia, use of continuous positive airway pressure (CPAP) ventilation has been advocated for the treatment of hypoxia associated with one-lung ventilation.[12 40] However, this interferes with surgical exposure and often re-insufflation of carbon dioxide is required before proceeding with surgery. Alternatively, significant intraoperative hypoxaemia has been shown to be corrected easily by administering one or two gentle ventilations to the collapsed lung. This procedure promptly improves Sp_{O_2} without interfering with the surgical field.[29]

Tracheal tube

Compared with the endobronchial technique, during anaesthesia with a tracheal tube continuous positive intrapleural pressure results in a reduction in the transpulmonary pressure gradient across the operative lung. Therefore, a greater percentage of the ventilator generated tidal volume enters the contralateral lung. Furthermore, as the lung is only partially collapsed, pulmonary hypoxic vasoconstriction remains intact and thus contributes to the improved oxygenation associated with anaesthesia with a tracheal tube.[41]

In a study of 719 cases undergoing anaesthesia with a tracheal tube for transthoracic electrocautery of the sympathetic chain, Lee, Seok-Mun and Lin administered 100% oxygen in combination with isoflurane and reported an Sp_{O_2} >99% throughout the operative procedure.[33] However, administration of 30% inspired oxygen in nitrous oxide resulted in an Sp_{O_2} of 93–96%. By increasing FI_{O_2} to 0.4–0.5, Sp_{O_2} stabilized to >98% in all patients.[41] Therefore, we suggest an initial FI_{O_2} of 0.4%, careful oximetric monitoring and adjustment of the inspired oxygen concentration to maintain an Sp_{O_2} >98%.

CARBON DIOXIDE INSUFFLATION

Rapid and excessive carbon dioxide insufflation into the closed chest cavity may create a tension pneumothorax, displace the mediastinum, and compress the lungs and great vessels with consequent haemodynamic instability. During carbon dioxide insufflation using endobronchial intubation, Hartrey and colleagues[26] reported a decrease in systolic arterial pressure of >20 mm Hg in 21% of patients. Similarly, we have reported sudden hypotension and bradycardia after injudicious carbon dioxide insufflation.[30] Therefore, both the anaesthetist and surgeon should be aware of this complication and excessive carbon dioxide insufflation avoided. Irrespective of the technique used, insufflation of up to 1 litre is usually sufficient to collapse the ipsilateral lung without inducing unwanted adverse effects.[41]

After accidental Verres' needle-induced lung puncture, carbon dioxide is insufflated directly into the lung parenchyma and bronchi. As the insufflation rate is greater than the predicted carbon dioxide production during uncomplicated anaesthesia,[39] this is readily diagnosed from the capnogragh waveform (fig. 1) and end-tidal carbon dioxide concentration.[41]

CARDIAC COMPLICATIONS

Although extremely rare, sudden cardiac arrest has been reported after left T2–3 sympathetic nerve transection. While the exact pathophysiology of this occurrence is unclear, it is postulated that before complete transection of the sympathetic trunk, continuous sympathetic stimulation to the stellate ganglions results in a reduction in the ventricular fibrillation threshold, arrhythmia and consequent cardiac arrest.[36]

In an interesting study of the delayed cardiac effects of T2–4 sympathectomy, Drott and colleagues demonstrated significantly reduced heart rate at rest, and during both exercise and the recovery phase of exercise. While systolic arterial pressure was reduced similarly, there was no significant reduction in diastolic arterial pressure.[18] Changes in the electrical axis and shortening of the QT interval have also been reported.[42] These results formed the basis for surgical cardiac sympathetic denervation in selected patient populations.[55]

Anaesthetic drug administration

Thoracoscopic electrocauterization of the sympathetic chain is usually an extremely short procedure. Therefore, anaesthetic drugs administered should be potent and short acting with few associated unwanted side effects. While inhalation anaesthetic agents are cheap and easy to administer, total i.v. anaesthesia with propofol has the theoretical advantage of not attenuating hypoxic vasoconstriction during one-lung ventilation.[21] Using a tracheal tube and total i.v. anaesthesia with propofol, alfentanil and atracurium in combination with 40% oxygen in air, no significant decrease in Sp_{O_2} was noted during carbon dioxide insufflation and partial collapse of the ipsilateral lung.[25] However, these positive finding are possibly FI_{O_2} dependent and not related to propofol administration.

Our anaesthetic of choice includes i.v. administration of fentanyl 5–7 $\mu g\ kg^{-1}$, propofol 1–2 mg kg^{-1} and atracurium 20–40 mg for induction of general anaesthesia. Thereafter, anaesthesia is maintained with 0.5–1.0 MAC of isoflurane and 50–60% nitrous oxide in oxygen. On conclusion of the surgical procedure the anaesthetic agents are discontinued, 100% oxygen administered and residual neuromuscular block antagonized with neostigmine and atropine.

Monitoring

In common with other surgical procedures, routine monitoring during thoracoscopic sympathectomy should include ECG, pulse oximetry and capnograghy. However, during thoracoscopic surgery, Sp_{O_2}

and end-tidal carbon dioxide have the additional function of monitoring the surgical technique.

Failure to observe an increase in end-tidal carbon dioxide during the insufflation phase indicates that the Verres' has been placed incorrectly. Furthermore, accidental lung puncture by the Verres' needle is easily recognized by a sudden steep increase in end-tidal carbon dioxide and from the classic waveform seen on the capnograph monitor (fig. 1). Finally, a sudden decrease in end-tidal carbon dioxide during carbon dioxide insufflation should raise suspicion of insufflator-induced tension pneumothorax and consequent decrease in pulmonary blood flow.[41]

As thorascopic sympathectomy is always associated with lung collapse and consequent $\dot{V}/\dot{Q}$ mismatching, pulse oximetry is mandatory during this procedure. Early diagnosis and adequate management of hypoxaemia during one-lung ventilation or after re-inflation of the operative lung requires both vigilance and ability to titrate FI_{O_2} against monitored Sp_{O_2}.

Postoperative care

The major postoperative concerns include exclusion of residual pneumothorax and haemothorax, and adequate treatment of postoperative pain (table 2). In the majority of cases the postoperative period is uneventful and after an overnight admission patients are routinely discharged. As clinical decisions are often based on radiological findings, postoperative chest x-ray is mandatory.

Irrespective of the technique used the reported incidence of postoperative pneumothorax is variable, occurring in 2–15% of cases.[48] As the lung is re-inflated under direct vision and the endoscope removed only when the lung is seen to bulge into it, this variability is probably technique dependent. In cases where residual pneumothorax is diagnosed, the extent of lung collapse should determine the need for intercostal drain. In a study by Gothberg, Drott and Claes,[23] postoperative chest x-ray after 1274 procedures in 602 patients demonstrated that a small apical pneumothorax (5±1 mm) was a usual occurrence. However, in only 0.8% of cases, because of expanding pneumothorax, was overnight chest drainage instituted. In our experience as most pneumothoraces are small, the decision to insert a chest drain depends on specific patient and physician tolerance and radiological evidence of expansion.

Haemothorax appears to be a relatively rare occurrence and is usually diagnosed by a combination of clinical signs and postoperative chest x-ray findings (table 2). Management decisions are patient specific.

Postoperative pain is common and most severe in the first 2–4 h after operation. As pain is generally retrosternal or in the upper back region and is not related to the incision, the exact mechanism is unclear. It has been suggested that carbon dioxide insufflation and consequent displacement of the mediastinum results in stretching of the pleura and activation of pain pathways.[22] While pain is adequately managed by postoperative opioid administration,[33,48] intrapleural catheters and local anaesthetic injection have had some success.[22,33] However, because of the possible danger of bilateral phrenic nerve block,[4] intrapleural local anaesthetic agents should be administered cautiously.[31] Non-steroidal anti-inflamatory drugs (NSAID) may provide an attractive alternative to opioids in the treatment of post-thoracospy pain. However, because of their slow onset of action, variable efficacy[52] and short duration of endoscopic sympathectomy, we have been unimpressed by NSAID-induced analgesia after endoscopic sympathectomy.

Table 2 Postoperative complications after anaesthesia with a tracheal tube compared with the endobronchial technique

Reference	Anaesthetic technique	Complication	Incidence/Cases performed
Jedeikin and colleagues[31]	Endobronchial	Pneumothorax, no ICD	8/58
		Haemothorax and ICD	2/58
		Subcutaneous emphysema	2/58
		Transient Horner's	2/58
Drott and colleagues[18]	Tracheal tube	Pneumothorax	5/535
		Haemothorax and ICD	1/535
		Postop. bradycardia	2/18
		Systolic arterial pressure	1/18
Hartrey and colleagues[26]	Endobronchial	Hypotension	
		Lung collapse	10/26
		Lung expansion	8/26
		Pneumothorax and ICD	2/26
Shachor and colleagues[48]	Endobronchial	Pneumothorax, no ICD	5/150
		Pneumothorax and ICD	2/150
		Haemothorax	3/150
		Subcutaneous emphysema	8/150
		Transient Horner's	2/150
Lee and colleagues[36]	Tracheal tube	Pneumothorax and ICD	1/719
		Haemothorax and ICD	7/719
		Scrotal emphysema	1/719
Lin and colleagues[36]	Tracheal tube	Cardiac arrest	2/719
Olsfanger and colleagues[41]	Tracheal tube	Hypotension	3/79
		Lung puncture	6/79
		Pneumothorax and ICD	3/79
		Haemothorax and ICD	2/79

In our experience adequate intraoperative analgesia significantly reduces the troublesome problem of postoperative pain and analgesic requirements.

Conclusion

Because of the anaesthetic implications and possible surgical complications, many surgeons are reluctant to perform transthoracic sympathectomy. However, this fear is poorly supported by the literature. Both in our experience, and from published data, it would appear that this procedure is safe and effective for treating palmar hyperhidrosis.

With the introduction of anaesthesia using a tracheal tube and use of a variable flow carbon dioxide insufflator, intraoperative airway management has been simplified and the incidence of hypoxia associated with one-lung ventilation decreased.

In conclusion, thorascopic sympathectomy is a simple and easy procedure associated with little cosmetic morbidity and few postoperative complications. Furthermore, in an era of soaring medical expenditure this procedure has the additional advantages of providing bilateral relief of the disabling symptoms while requiring few preoperative investigations, a "same day" admission and short hospital stay.

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British Journal of Anaesthesia 1997; 79: 120–121

SHORT COMMUNICATIONS

Extradural buprenorphine suppresses breast feeding after Caesarean section

M. HIROSE, T. HOSOKAWA AND Y. TANAKA

Summary

Satisfactory pain relief with postoperative extradural bupivacaine increases the amount of breast feeding after Caesarean section. To investigate the effect of extradural buprenorphine, we have evaluated the amount of breast feeding and the gain in infant weight for 11 days after Caesarean section in patients who received continuous extradural bupivacaine with or without buprenorphine. Extradural buprenorphine significantly decreased both measures although there was no significant difference in pain intensity. We suggest that extradural buprenorphine suppressed breast feeding after Caesarean section. (*Br. J. Anaesth.* 1997; **79**: 120–121).

Key words
Anaesthesia, obstetric. Analgesic techniques, extradural. Analgesics opioid, buprenorphine. Pain, postoperative.

Our recent investigation revealed that satisfactory postoperative pain relief with continuous extradural bupivacaine for 3 days after Caesarean section improved the amount of breast feeding and gain in infant weight compared with unsatisfactory pain relief without extradural analgesia.[1] Although extradural opioids are also known to provide satisfactory analgesia after Caesarean section,[2 3] the effect of extradural opioids on breast feeding has not been evaluated. Extradural bupivacaine has less effect on the neurobehavioural state of the neonate than other local anaesthetics or opioids.[4 5] Opioids such as pethidine[6] induce neurobehavioural depression in the neonate. We hypothesized that extradural opioids would suppress breast feeding while providing satisfactory postoperative pain relief. To evaluate the effect of extradural buprenorphine, we measured the amount of breast feeding and gain in infant weight for 11 days in patients who received continuous extradural bupivacaine with or without buprenorphine for 3 days after Caesarean section.

Methods and results

After obtaining approval from the hospital Ethics Committee and written informed consent, we studied two groups of full-term parturients (without co-existing disease) who had undergone elective Caesarean section under spinal and extradural anaesthesia. Indications for Caesarean section were previous Caesarean section, breech presentation and predicted cephalopelvic disproportion. Patients were allocated randomly to one of two groups to receive extradural bupivacaine alone (control group, $n=10$) or extradural bupivacaine and buprenorphine (buprenorphine group, $n=10$) for postoperative pain management.

All patients were premedicated with metoclopramide 10 mg i.v., 1 h before operation. After the patient received an i.v. infusion of lactated Ringer's solution 1–1.5 litre, the extradural catheter was placed at the T12–L1 or L1–2 interspace, and then 0.3% cinchocaine 1.2–1.8 ml was given intrathecally using a 26-gauge disposable spinal needle into the L3–4 or L4–5 interspace. In the control group, patients were given 0.25% bupivacaine 5 ml extradurally as a loading dose after clamping of the umbilical cord, followed by continuous infusion of 0.25% bupivacaine 0.7 ml h^{-1} using a disposable balloon-operated infuser (Sure-fuser SFA-0503D, Nipro, Japan) for 3 days for pain relief. In the buprenorphine group, patients were given 5 ml of 0.25% bupivacaine with buprenorphine 200 μg extradurally after clamping of the umbilical cord, followed by continuous infusion of 0.25% bupivacaine 0.7 ml h^{-1} containing buprenorphine 12 μg ml^{-1}. Diclofenac suppository 25 mg was available on demand for supplementary analgesia in both groups.

All patients started breast feeding when they were able to assume a sitting position after operation, and were encouraged to nurse every 4 h. The weight of milk fed by breast and infant weight were measured for 11 days. To measure the weight of milk fed by breast, each mother weighed her baby on the scales before and after nursing. All babies wore a nappy during nursing to prevent underestimation of the weight caused by urination. Pain intensity both at rest and at coughing was assessed using a visual analogue scale (0 cm=no pain, 10 cm=worst imaginable pain) at three times: 2 h after operation, 1 and 2 days in the morning after operation.

Two-way ANOVA for repeated measures was used for inter-group comparisons. After testing

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MUNETAKA HIROSE, MD, TOYOSHI HOSOKAWA, MD, YOSHIFUMI TANAKA, MD, Department of Anaesthesiology, Kyoto Prefectural University of Medicine, Kamigyoku, Kyoto 602, Japan. Accepted for publication: March 4, 1997.

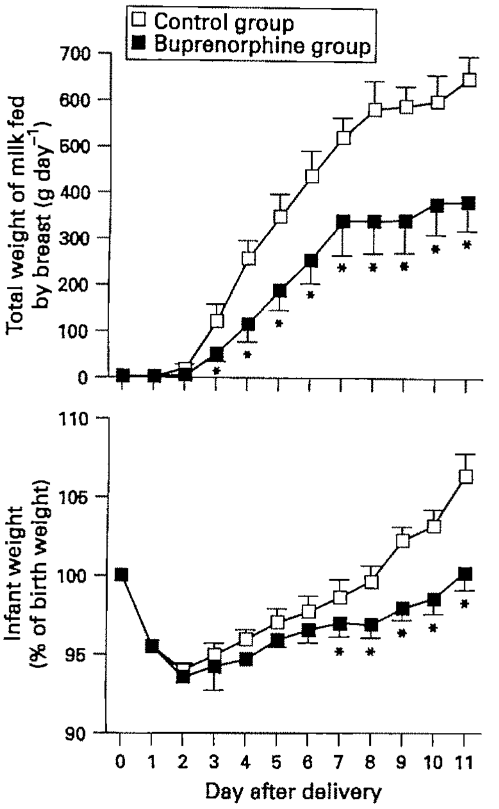

Figure 1 Time course of the extent of breast feeding and change in infant weight, expressed as a percentage of birth weight, after delivery. Patients in the control group (n=10) received postoperative pain management with extradural bupivacaine and patients in the buprenorphine group (n=10) received extradural bupivacaine and buprenorphine. Data are mean (SEM). *Significantly different from corresponding value in the control group.

significant differences, Fisher's least significant difference test was used to identify significant differences in various pairs of comparisons. The null hypothesis was rejected when $P<0.05$. All values are reported as mean (SEM).

There were no differences in age, weight or height of parturients, or neonatal birth weight. Number of primiparous/multiparous women was 7/3 in the control group and 6/4 in the buprenorphine group. All multiparous women had previously breast fed successfully. Apgar scores in all neonates at 1 and 5 min were 8–10. Visual analogue scale scores 2 h, 1 and 2 days after operation at rest were: 15.6 (8.2), 15.0 (5.3) and 9.3 (4.4) mm in the control group and 16.0 (6.0), 7.4 (3.8) and 4.1 (2.9) mm in the buprenorphine group. Visual analogue scale scores on coughing were 23.8 (9.8), 36.7 (8.9) and 32.0 (8.6) mm in the control group and 16.0 (7.3), 33.2 (5.1) and 27.5 (7.5) mm in the buprenorphine group. There were no significant differences in scores between the groups. Total dose of diclofenac for 3 days after operation in the buprenorphine group was 5 (5) mg, which was significantly less than that in the control group (25 (8) mg). In the control group, five patients required diclofenac compared with one patient in the buprenorphine group. Both the extent of breast feeding and gain in infant weight were significantly suppressed in the buprenorphine group compared with the control group (fig. 1).

Comment

We found that extradural buprenorphine added to bupivacaine decreased both the weight of milk fed by breast and gain in infant weight compared with extradural bupivacaine alone, even though it provided satisfactory pain relief and reduced the dose of supplementary analgesics. Buprenorphine, a highly lipid-soluble opioid partial agonist, can easily cross the lipid membrane in the mammary gland from the intravascular space and can affect not only the maternal but also the neonatal central nervous system. We suggest that extradural buprenorphine suppressed breast feeding. Further study is needed to evaluate the effect of other extradural opioids, such as morphine, fentanyl and pethidine, on breast feeding after Caesarean section.

Postoperative pain relief for only 3 days affects breast feeding for up to 11 days after Caesarean section.[1] This study also showed that the effect of extradural buprenorphine for 3 days on breast feeding continued for up to 11 days after Caesarean section. Therefore, maternal postoperative pain relief after Caesarean section could be an important factor in infant development.

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Administration of magnesium sulphate before rocuronium: effects on speed of onset and duration of neuromuscular block

B. KUSSMAN, G. SHORTEN, J. UPPINGTON AND M. E. COMUNALE

Summary

The speeds of onset of pancuronium, atracurium and vecuronium are increased by prior administration of magnesium sulphate. A prospective, randomized, double-blind, controlled, clinical study was performed to examine the effects of prior i.v. administration of magnesium sulphate 60 mg kg^{-1} on the neuromuscular blocking effects of rocuronium 0.6 mg kg^{-1} during isoflurane anaesthesia. Neuromuscular function was measured electromyographically (Relaxograph) in 30 patients who received either magnesium sulphate 60 mg kg^{-1} or normal saline, 1 min before rocuronium 0.6 mg kg^{-1}. Mean onset times were similar in the two groups (magnesium sulphate 71 (SD 20) s; normal saline 75 (23) s), but times to initial, 10% and 25% recovery from neuromuscular block were significantly longer in the magnesium sulphate group (42.1 (16.3), 49.0 (12.4) and 56.5 (13.2) min, respectively) than in the saline group (25.1 (9.1), 33.0 (11.1) and 35.6 (13.2) min, respectively) ($P<0.05$ in all three cases). Administration of magnesium sulphate was not associated with adverse haemodynamic effects. Prior administration of magnesium sulphate, under the study conditions described, prolonged rocuronium-induced neuromuscular block but did not increase speed of onset. (*Br. J. Anaesth.* 1997; **79**: 122–124).

Key words
Ions, magnesium. Pharmacology, magnesium sulphate. Neuromuscular block, rocuronium. Neuromuscular block, measurement of response.

The action of non-depolarizing neuromuscular blockers is potentiated by magnesium sulphate ($MgSO_4$)[1] and the speeds of onset of pancuronium, atracurium and vecuronium are increased by prior administration of $MgSO_4$.[2-4] The aims of this study were to determine the effects of prior administration of $MgSO_4$ 60 mg kg^{-1} i.v. on the onset and duration of rocuronium-induced neuromuscular block, and to quantify the haemodynamic effects of bolus i.v. administration of $MgSO_4$ 60 mg kg^{-1} on heart rate and arterial pressure.

Methods and results

After obtaining Institutional Review Board approval and written informed consent, we studied 30 ASA I or II patients, aged 18–65 yr, undergoing surgery requiring tracheal intubation. A prospective, randomized, double-blind study was performed.

Patients received midazolam <0.05 mg kg^{-1} i.v. as premedication if indicated clinically. After 3 min of preoxygenation, anaesthesia was induced with thiopentone 4 mg kg^{-1} and fentanyl 1.5 μg kg^{-1}, and maintained with 1–1.5% isoflurane (inspired concentration) and 66% nitrous oxide in oxygen.

The response of the first dorsal interosseous muscle of the hand to supramaximal train-of-four (TOF) stimulation of the ulnar nerve at the wrist at 10-s intervals was measured electromyographically (Relaxograph, Datex Instrumentarium, Helsinki, Finland). The forearm was wrapped with a cotton blanket to minimize cooling. After induction of anaesthesia and having established a stable twitch response (at least three successive equal responses to TOF stimulation), either $MgSO_4$ 60 mg kg^{-1} or normal saline (NaCl) was given i.v. over 1 min according to random allocation. One minute after completion of this infusion, rocuronium 0.6 mg kg^{-1} was administered via a fast flowing i.v. infusion over 5 s. The times to 90% (T1=10%) and complete (T1=0%) single twitch depression, and to initial, 10% and 25% spontaneous recovery were measured. Heart rate and arterial pressure were measured immediately before and after induction of anaesthesia, 30 s after administration of $MgSO_4$ 60 mg kg^{-1} or NaCl, and at 1-min intervals for 3 min after administration of rocuronium (Hewlett Packard Component System, Andover, MA, USA). The minimum nasopharyngeal temperature measured with a thermistor temperature probe during the study was recorded (Hewlett Packard, part no. 21075A, Andover, MA, USA).

Sample size was calculated based on the following: taking the level of statistical significance as alpha=0.05 and beta=0.2, where 1−beta=the

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BARRY KUSSMAN, MB, BCH, FFA(SA), GEORGE SHORTEN, MD, JEFFREY UPPINGTON, MD, MARK E. COMUNALE, MD, Department of Anaesthesia and Critical Care, Beth Israel Hospital, and Harvard Medical School, Boston, MA 02215, USA. Accepted for publication: March 6, 1997.

Correspondence to G. S.

power of the study, a difference of 20% between two groups in onset time was sought.

Effect size (onset time) = 108* s×20% = 21.6.

Standardized effect size = effect size/SD = 21.6/24* = 0.9.

*Based on previous data.[5]

Data were analysed using unpaired (pharmacodynamic variables) and paired (within-patient comparison of heart rate and arterial pressure) two-tailed Student's t tests. Significance was defined as $P<0.05$.

The two groups were similar in age, weight, sex distribution and minimum nasopharyngeal temperature. Mean onset times to T1 = 10% ($MgSO_4$ 71 (SD 20) s, NaCl 75 (23) s) and T1 = 0% ($MgSO_4$ 105 (36) s, NaCl 107 (30) s) were similar in the two groups. The time to initial recovery was longer in the $MgSO_4$ group (42.1 (16.3) min) compared with the NaCl group (25.1 (9.1) min) (fig. 1). Similarly, times to 10% and 25% single twitch recovery in the $MgSO_4$ group (49.0 (12.4) and 56.5 (13.2) min, respectively) were greater than those in the NaCl group (33.0 (11.1) and 35.6 (13.2) min, respectively) (fig. 1).

Recovery data to 25% twitch suppression were not obtained in two patients. One patient with normal renal function, who received $MgSO_4$ and who was not receiving magnesium-containing medications, had a markedly prolonged block. The first evidence of spontaneous recovery occurred 65 min after administration of rocuronium. Plasma magnesium concentration was 4.0 mmol $litre^{-1}$, 75 min after administration of $MgSO_4$ 60 mg kg^{-1}; baseline plasma magnesium concentration had not been obtained. The Relaxograph was accidentally disconnected in the second (NaCl group) patient during complete ablation of twitch response. Although arterial pressures were similar in the two groups throughout the study, heart rates in the $MgSO_4$ group were significantly greater than those in the NaCl group immediately after induction of anaesthesia (mean 83 (SD 9) and 74 (10) beat min^{-1}, respectively; $P=0.014$), after administration of $MgSO_4$ or NaCl (92 (12) and 78 (16) beat min^{-1}, respectively; $P=0.013$), and 1 min after administration of rocuronium (91 (11) and 77 (16) beat min^{-1}, respectively; $P=0.01$).

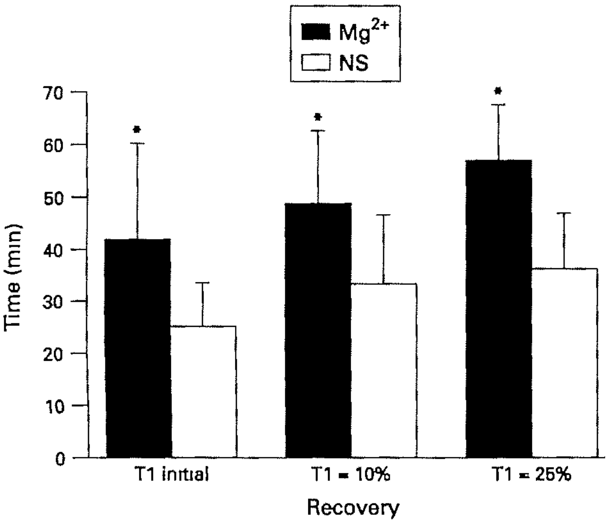

Figure 1 Times to initial recovery (T1 initial) and to T1 = 10% and T1 = 25% in the magnesium sulphate (Mg^{2+}) and normal saline (NS) groups. *$P<0.05$.

Comment

We have demonstrated that prior administration of $MgSO_4$ did not increase speed of onset, but prolonged duration of action of rocuronium-induced (0.6 mg kg^{-1}) neuromuscular block.

In the presence of high concentrations of magnesium, fewer calcium ions bind to acetylcholine containing vesicles, thus decreasing acetylcholine release from the nerve ending.[6] Postsynaptically, magnesium ions may compete with calcium ions for activation sites on the myosin ATPase necessary for excitation–contraction coupling.[7]

Previous studies of the effect of $MgSO_4$ on onset times for non-depolarizing neuromuscular blocking agents have produced conflicting results.[2–4] It appears that the shorter the "baseline" onset time, the less effect $MgSO_4$ pretreatment has on its reduction. This may be because the time of delivery of the neuromuscular blocking agent is unaffected. The remaining portion of onset time, which can be influenced by the pharmacodynamic effect of $MgSO_4$, is short, approximately 30–40 s. Similar proportionate decreases in onset time result in smaller absolute effects for fast compared with slow onset agents. For example, administration of $MgSO_4$ 60 mg kg^{-1} before pancuronium 0.1 mg kg^{-1} resulted in a fast onset time (68.3 (25.9) s). The results of this study are consistent with those of others who have shown that prior administration of $MgSO_4$ consistently prolongs neuromuscular block induced by intermediate-acting, non-depolarizing neuromuscular blocking agents.[3 4] In contrast, $MgSO_4$ 60 mg kg^{-1} did not prolong the neuromuscular blocking effects of pancuronium 0.1 mg kg^{-1}.[2] One possible explanation is that the effects of a bolus dose of $MgSO_4$ are diminished by the time that spontaneous recovery from the longer acting pancuronium begins to take place. The differences in heart rate between the $MgSO_4$ and NaCl groups immediately after induction of anaesthesia were not clinically significant. The small samples used in this study increased the likelihood of encountering such a difference randomly.

In summary, $MgSO_4$ did not increase the speed of onset, but prolonged the duration of rocuronium-induced neuromuscular block. Administration of $MgSO_4$ at this dose before rocuronium offered no clinical advantage and because an unanticipated, prolonged neuromuscular block could result, is potentially harmful.

Acknowledgements

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Dystrophin deficient *mdx* muscle is not prone to MH susceptibility: an *in vitro* study

N. MADER, H. GILLY AND R. E. BITTNER

Summary

The association between malignant hyperthermia (MH) and neuromuscular disorders is controversial. An association between MH and Duchenne muscular dystrophy, a common and lethal disorder caused by deficiency of dystrophin, has been reported sporadically but is still not proved. To examine this problem, we performed halothane and caffeine *in vitro* contracture tests on skeletal muscles from dystrophin deficient *mdx* mice, an animal model for human Duchenne muscular dystrophy. As neither halothane nor caffeine triggered abnormal responses in *mdx* muscles, we conclude that dystrophin deficiency *per se* is not the primary cause of MH-like crises, as reported for patients with Duchenne muscular dystrophy. (*Br. J. Anaesth.* 1997; **79**: 125–127).

Key words
Malignant hyperthermia. Model, mouse. Complications, muscular dystrophy.

On the basis of sporadic clinical reports[1 2] an association between malignant hyperthermia (MH) has been described and several neuromuscular disorders, such as central core disease, King-Denborough syndrome, several myotonic disorders and several forms of muscular dystrophies, including Duchenne muscular dystrophy. Duchenne muscular dystrophy is an X-linked lethal muscle disorder (with an incidence of approximately 1 in 3500 male births) caused by lack of, or reduction in, dystrophin, a 427-kDa spectrin-like protein which is expressed at the inner surface of the plasma membranes of skeletal and cardiac muscle fibres.[3] In the mouse model for Duchenne muscular dystrophy (*mdx* mutant mouse), dystrophin deficiency causes only mild myopathy without clinically overt symptoms. In both conditions, human Duchenne muscular dystrophy and murine *mdx*, defective intracellular calcium homeostasis, leading to increased sarcoplasmic calcium concentrations, is considered to arise from defective muscle fibre membranes caused by deficiency of dystrophin.[1 3] Defective sarcoplasmic calcium homeostasis is also thought to be the pathophysiological basis of MH,[1 2 4 5] a hypermetabolic crisis, characterized by a rapid increase in temperature, hypercontractility and rigidity of muscles, in addition to respiratory and metabolic acidosis.[1 2] In susceptible patients, MH is triggered by inhalation anaesthetic agents (e.g. halothane) and depolarizing neuromuscular blocking agents (e.g. suxamethonium).[2 4] Although in some MH pedigrees, mutations within the ryanodine receptor gene (RYR1)[4 5] encoding a calcium regulatory membrane protein have been identified, the molecular basis is not clear for the majority of MH patients.[1] Thus defective sarcoplasmic calcium homeostasis is common to both dystrophin deficiency and RYR1 mutations. Because Duchenne muscular dystrophy is one of the most common and severe neuromuscular disorders, we carried out this study in order to determine if dystrophin deficiency and concomitant defective calcium homeostasis leads to increased MH susceptibility. For this purpose we performed *in vitro* contracture tests (IVCT) on dystrophin deficient *mdx* muscle and on normal mouse muscle.

Methods and results

Ten male C57BL/10ScSnHim*mdx* mice and 10 male normal mice (C57BL/10ScSnHim) were killed by cervical dislocation at the age of 10 weeks. Dystrophin status of *mdx* and normal mouse muscle was determined by immunohistochemistry and by Western blotting, using a dystrophin specific polyclonal antiserum raised in sheep, directed against the 60-kDa dystrophin fusion protein.[3] Immediately after cervical dislocation, both extensor digitorum longus (EDL) muscles were excised and immersed in modified Krebs–Ringer solution which was gassed continuously with 95% oxygen and 5% carbon dioxide. IVCT were performed, exposing one muscle to halothane and the contralateral muscle to caffeine. In order to accommodate for the small mouse muscles (approximate weight 0.02 g), the standard procedure of the European Malignant Hyperthermia Group[6] was modified slightly (pre-drug resting tension approximately 1 g). Muscle viability was

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NINA MADER, MD, REGINALD E. BITTNER, MD, Institute of Anatomy, Neuromuscular Research Department, University of Vienna, Waehringerstraße 13, A-1090-Vienna, Austria. HERMANN GILLY, PHD, Department of General Anaesthesia and Intensive Care Medicine (B), University of Vienna and L. Boltzmann Institute for Experimental Anaesthesia and Research in Intensive Care Medicine, A-1090-Vienna, Austria.
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Correspondence to R. E. B.

tested by electrical stimulation (repetition rate 0.2 Hz; pulse width 1 ms; constant current approximately 80 mA). Halothane was added to the gas-flow to achieve a final concentration of 0.11, 0.22, 0.44 and 0.66 mmol litre^{-1}, using an agent-specific vaporizer (Vapor 3.1, Dräger, Germany). Caffeine concentrations were increased cumulatively (0.5, 1, 2, 3 and 4 mmol litre^{-1}). When, after a stabilization period ($\geqslant$20 min), resting tension did not decrease by more than 0.04 mN min^{-1}, halothane and caffeine tests were started. Contractile force was evaluated from the chart records by calculating the respective drug-induced increase, that is the difference between the highest contracture which was observed within 3 min after drug administration and pre-drug force of contraction. At the end of the test, the viability of the muscles was tested using caffeine concentrations of 32 mmol litre^{-1}. As all muscles tested responded with tetanic contractures they were considered viable (tables 1, 2).

EFFECT OF HALOTHANE IVCT ON *MDX* (N=*10*) AND NORMAL MUSCLES (N=*10*)

In *mdx* muscles there were no dose-dependent increases in muscle contractures after adding halothane (table 1).

In EDL muscles from normal mice, before and after adding the drugs, transient and dose-independent increases in contractile force were recorded in three of 10 muscles exposed to halothane. However, within 1–3 min, the contractures re-stabilized at pre-drug baseline values. Apart from these transient contractures there were no increases produced by halothane.

At the end of the experiments muscle viability was tested in both groups by adding caffeine 32 mmol litre^{-1}. All muscles responded with tetanic contractures. In these tests *mdx* muscles responded with an average increase of 3.2 g, while control muscles responded with an average increase of 5.7 g (table 1).

EFFECT OF CAFFEINE IVCT ON *MDX* (N=*8*) AND NORMAL MUSCLES (N=*10*)

The caffeine test was carried out on eight of 10 *mdx* muscle specimens and no dose-dependent increases in muscle contracture were observed (table 2).

In five of 10 control muscles, transient and dose-independent increases in contractile force were recorded, as described above.

Tetanic contractures produced by addition of caffeine 32 mmol litre^{-1} at the end of the experiments

Table 1 Halothane *in vitro* contracture tests using EDL muscles from dystrophin deficient *mdx* mice (*mdx*) and from normal mice (control). All values for twitch height and contracture force are in grams. Responses to cumulative administration of halothane 0.11–0.66 mmol litre^{-1} are maximum increases above pre-drug levels. These responses are indicated as negative (neg.) or transient, dose-independent contractures, which decreased to baseline within 1–3 min; >=outside the range of recording. The response to caffeine 32 mmol litre^{-1} of control mouse No. 9 is indicated by ">1 g" because the muscle bundle tore in the presence of caffeine 32 mmol litre^{-1}

Animal No.	Pre-drug twitch height		+Halothane (0.11–0.66 mmol litre^{-1})		+Caffeine 32 mmol litre^{-1}	
	mdx	Control	*mdx*	Control	*mdx*	Control
1	0.1	0.2	neg.	neg.	3	>7
2	0.15	0.2	neg.	+0.5→neg.	>7.7	>8.4
3	0.2	0.2	neg.	+0.5→neg.	>7.8	>7.5
4	0.02	0.15	neg.	neg.	2.4	6.5
5	<0.1	0.15	neg.	neg.	1.6	5.8
6	0.05	0.2	neg.	+0.3→neg.	3.1	>7.8
7	<0.1	0.1	neg.	neg.	1.6	5.6
8	<0.1	0.1	neg.	neg.	1.7	7
9	<0.1	<0.01	neg.	neg.	1.6	>1
10	<0.1	<0.1	neg.	neg.	1.9	0.7

Table 2 Caffeine *in vitro* contracture tests using EDL muscles from dystrophin deficient *mdx* mice (*mdx*) and from normal mice (control). All values for twitch height and contracture force are in grams. Responses to cumulative administration of caffeine 0.5–4.0 mmol litre^{-1} are maximum increases above pre-drug levels. These responses are indicated as negative (neg.) or transient, dose-independent contractures, which decreased to baseline within 1–3 min; >=outside the range of recording. EDL muscles from *mdx* mice Nos 4 and 9 were not reliable (nr) because the baseline did not stabilize within 20 min of the pre-drug period

Animal No.	Pre-drug twitch height		+Caffeine (0.5–4.0 mmol litre^{-1})		+Caffeine 32 mmol litre^{-1}	
	mdx	Control	*mdx*	Control	*mdx*	Control
1	0.05	0.5	neg.	+0.6→neg.	1.7	>5
2	0.15	0.15	neg.	neg.	5.6	>2.5
3	<0.1	0.25	neg.	+0.3→neg.	0.6	>5.7
4	n.r.	0.3	n.r.	neg.	n.r.	3
5	0.1	0.2	neg.	+0.1→neg.	1.5	4
6	0.1	0.1	neg.	+0.2→neg.	1.8	4.5
7	<0.1	0.1	neg	+0.1→neg.	2.4	4.5
8	0.1	0.15	neg.	neg.	1.4	4
9	<0.1	0.02	nr	neg.	nr	1.6
10	0.05	0.15	neg.	neg.	1.5	7.3

were demonstrable in both *mdx* and normal muscle specimens. The *mdx* muscles responded with an average increase of 2.1 g while the control muscles responded with an average increase of 4.2 g (table 2).

Comment

We have used the dystrophin deficient *mdx* mouse, a valid and commonly accepted animal model for Duchenne muscular dystrophy, to study if dystrophin deficiency in human Duchenne muscular dystrophy is causative for the MH-like crises which have been observed sporadically in patients with Duchenne muscular dystrophy.[1 2] Using an *in vitro* assay (i.e. IVCT) as recommended by the European MH Group[6] for MH diagnosis, we found no abnormal reactions in *mdx* muscles after exposure to either halothane or caffeine. These data strongly indicate that there is no increased MH susceptibility in dystrophin deficient *mdx* mouse muscle. Normal and dystrophic mouse muscles fulfilled the viability criteria as all muscles tested responded to the addition of caffeine 32 mmol litre^{-1} at the end of the experiments with tetanic contractures. Moreover, muscles responded to electrical stimulation by reproducible twitches in the respective IVCT experiments. For *mdx* muscles we observed relatively small twitch responses during the pre-drug period and relatively small contractile forces after adding caffeine 32 mmol litre^{-1} compared with normal mouse muscles. This phenomenon is consistent with the findings of Coulton and colleagues that *mdx* muscle shows less twitch and tetanic tension compared with normal mouse muscle.[7]

Transient, short contractures, as occurred in normal mouse muscle (three of 10 muscles in the halothane test (table 1), five of 10 muscles in the caffeine test (table 2)) can also be seen sporadically in human muscles which are finally diagnosed as MH negative (MHN) (H. Gilly, unpublished data). Although it is difficult to define a threshold for normal mouse muscle we did not observe the phenomenon of spontaneous contractures in *mdx* muscle, indicating that *mdx* muscle fulfilled the "normality criteria" with respect to the IVCT protocol which was designed for human muscle samples. In this context we cannot determine if transient contractures are specific for the normal C57BL/10 mouse strain used. As neither halothane nor caffeine induced abnormal prolonged contractures in any normal or dystrophic muscle tested, we conclude that dystrophin deficiency *per se* is not the primary cause of increased MH susceptibility.

Defective calcium homeostasis, which is common to human Duchenne muscular dystrophy and *mdx* muscle, is considered to play a crucial pathophysiological role in MH.[2 4 5] This is corroborated by the finding that missense mutations affecting the calcium regulatory domain of the ryanodine receptor (RYR1) are associated with MH in humans and in pigs.[1 4 5] However, despite defective calcium homeostasis in dystrophin deficient *mdx* muscle, we did not observe any MH related changes during halothane–caffeine IVCT. Our findings cannot exclude the possibility that in human Duchenne muscular dystrophy muscle which is more severely affected by dystrophic changes and necrotic events compared with *mdx* muscle, there might be a threshold dependent mechanism with respect to increased intracellular calcium concentrations and consequent MH susceptibility. We conclude that mechanisms other than dystrophin deficiency should be considered in the aetiology of increased MH susceptibility in human Duchenne muscular dystrophy.

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Effects of ketamine and pentobarbitone on acetylcholine release from the rat frontal cortex *in vivo*

T. KIKUCHI, Y. WANG, H. SHINBORI, K. SATO AND F. OKUMURA

Summary

We have studied the effects of ketamine and pentobarbitone on acetylcholine (ACh) release from the rat frontal cortex using microdialysis. Ketamine 25, 50 and 100 mg kg^{-1} increased ACh release from the frontal cortex to 286%, 253% and 381% of basal release, respectively. In contrast, pentobarbitone 10, 20 and 40 mg kg^{-1} caused 73%, 78% and 96% inhibition of basal levels, respectively. The results suggest that ketamine and pentobarbitone have opposite effects on ACh release from the rat frontal cortex, as seen previously in the rat hippocampus. (*Br. J. Anaesth.* 1997; **79**: 128–130).

Key words

Nerve, neurotransmitters. Anaesthetics i.v., ketamine. Hypnotics barbiturate, pentobarbitone. Brain, cerebral cortex. Rat.

Cholinergic neurones, which are distributed widely in the brain, have been implicated in a variety of functions, such as memory, learning and motor function. However, the effects of various anaesthetics on cholinergic neurones are not well understood at the molecular level.

Recently, brain microdialysis techniques combined with HPLC-ECD have been well established for measurement of acetylcholine (ACh). In previous studies[1] using this microdialysis technique, we have already shown differential effects of ketamine and pentobarbitone on ACh release from rat hippocampus and striatum, and also demonstrated that the stimulating effect of ketamine might be involved in dopamine D_1 receptor mechanisms.

Determination of ACh release in brain regions such as the cortex, hippocampus, striatum or medial pontine reticular formation is relevant for the study of anaesthetic mechanisms as ACh is thought to be one of the important neurotransmitters involved in the action of anaesthetics.[2 3] The purpose of this study was to investigate the effects of ketamine and pentobarbitone on ACh release from the rat frontal cortex.

Methods and results

Microdialysis experiments were performed on 30 male adult Sprague–Dawley rats, weighing approximately 300 g, during free movement, at least 2 days after implantation of a microdialysis probe.[1] The study was approved by the Animal Welfare Committee of Yokohama City University School of Medicine. The animals, anaesthetized with sodium pentobarbitone 40 mg kg^{-1} i.p. were placed in a stereotaxic frame (Model SR-6, Narisige Scient Instrument LAB., Japan) and the intracerebral guide cannula (CMA 10, Carnegie Medicine, Sweden) was implanted stereotaxically into the right frontal cortex (coordinates taken from bregma with skull flat: A=3.3 mm, L=2.8 mm, V=0.5 mm from the atlas of Paxinos and Watson) and fixed in place using dental cement. The probes (CMA 11, Carnegie Medicine, Sweden) (2-mm long dialysis membrane, od 0.24 mm, molecular weight cut-off=20 000 Da) were perfused with Ringer's solution containing eserine sulphate 10 μmol $litre^{-1}$ (Wako Pure Chemical Industries Ltd., Japan), an inhibitor of choline esterase, at a rate of 2.0 μl min^{-1} using a microperfusion pump (Model CMA 102, Carnegie Medicine, Sweden). After pre-perfusion with Ringer's solution for 120 min, each sample was collected for 20 min in a cooled polyethylene tube containing 10 μl of ethylhomocholine 1 μmol $litre^{-1}$, an internal standard for high performance liquid chromatography (HPLC) determination. The test drugs were ketamine 25, 50 and 100 mg kg^{-1} i.p. (Sankyo Ltd., Japan) and pentobarbitone 10, 20 and 40 mg kg^{-1} i.p. (Abbott Laboratories, USA). After collecting three basal samples, the test drugs were administered i.p. ACh was assayed by a method described previously.[1] The limit of sensitivity was 100 fmol (100 fmol/50 μl injection). At the end of the experiments, the animals were killed with an overdose of diethyl ether, and the position of the probe in the brain was confirmed by visual examination.

Mean ACh recovery through the probes at a rate of 2 μl min^{-1} was 11.1 (SEM 0.7) % (n=5). ACh release was expressed as a percentage of basal values. Basal release was obtained from the mean of three initial collections before administration of the test drugs. The significance of differences between mean

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TATSUAKI KIKUCHI, MD, YANSHEN WANG, MD, HIRONOBU SHINBORI, MD, KAZUO SATO, MD, FUKUICHIRO OKUMURA, MD, Department of Anesthesiology, Yokohama City University School of Medicine, Yokohama 236, Japan. Accepted for publication: March 2, 1997.

Correspondence to F. O.

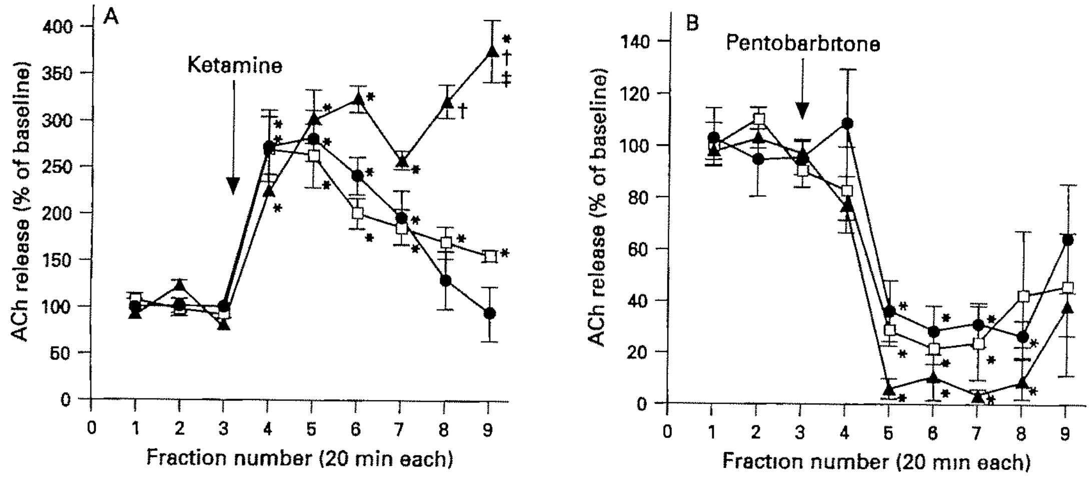

Figure 1 A: Effects of ketamine 25 mg kg^{-1} (●, $n=5$), 50 mg kg^{-1} (□, $n=5$) and 100 mg kg^{-1} (▲, $n=5$) i.p. on acetylcholine (ACh) release. *$P<0.05$ compared with pre-drug values; †$P<0.05$ compared with ketamine 25 mg kg^{-1}; ‡$P<0.05$ compared with ketamine 50 mg kg^{-1} according to ANOVA with *post hoc* Scheffé's *F* test. B: Effects of pentobarbitone 10 mg kg^{-1} (●, $n=5$), 20 mg kg^{-1} (□, $n=5$) and 40 mg kg^{-1} (▲, $n=5$) i.p. on acetylcholine (ACh) release. *$P<0.05$ compared with pre-drug values according to ANOVA with *post hoc* Scheffé's *F* test for multiple comparisons. Data are group mean (SEM)

values was determined by ANOVA with repeated measures, followed by Scheffé's *F* test for multiple comparisons. $P<0.05$ was considered statistically significant.

In this experiment, ketamine 25, 50 and 100 mg kg^{-1} i.p. and pentobarbitone 10, 20 and 40 mg kg^{-1} i.p. produced a sleeping state in all rats within 10 min which lasted throughout the experiment.

ACh release was stable over 120 min after the beginning of perfusion. Baseline ACh concentration from the frontal cortex in 20-min samples was 0.90 (SEM 0.07) pmol per sample ($n=30$).

Figure 1A shows the effects of ketamine on ACh release from the frontal cortex. Ketamine 25, 50 and 100 mg kg^{-1} i.p. increased ACh release from the frontal cortex. The maximum increases in ACh release produced by ketamine 25, 50 and 100 mg kg^{-1} i.p. were 286%, 253% and 381% of basal levels, respectively. The mean increase in ACh release reached a maximum value within 40 min after administration of ketamine 25 and 50 mg kg^{-1}; subsequently there was a gradual decrease. However, ACh produced by ketamine 100 mg kg^{-1} continued to increase over the entire experimental period representing a biphasic pattern.

In contrast, as shown in figure 1B, pentobarbitone 10, 20 and 40 mg kg^{-1} i.p. decreased ACh release from the frontal cortex. The maximal effects of pentobarbitone 10, 20 and 40 mg kg^{-1} i.p. were 73%, 78% and 96% inhibition of basal levels, respectively.

Comment

The frontal cortex comprises the motor area and the association area, the so called *prefrontal cortex*, that is concerned with concentration, attention, initiative and spontaneity. Both the frontal cortex and hippocampus receive cholinergic projections mainly from the anterior and posterior regions of the cholinergic basal nuclear complex, respectively.[4] Behavioural and pharmacological evidence suggests that regulation of cortical and hippocampal cholinergic activity is often similar. The increase in ACh release in the cortex reflects the desynchronized electroencephalogram (EEG) during wakefulness and REM sleep.[5]

Pentobarbitone decreased ACh release from the rat frontal cortex, as seen in the rat striatum and hippocampus,[1] which strongly supports the concept that pentobarbitone has a "depressant" anaesthetic effect. It is generally believed that various barbitones such as pentobarbitone produce marked and persistent enhancement of the function of the gamma-aminobutyric acid (GABA)$_A$ coupled chloride channel and reduce glutamate-induced depolarization. Furthermore, there is abundant evidence that barbitones depress cortical EEG activity, and cholinergic neural activity in the cortex correlates positively with cortical EEG activity,[3] which is in agreement with our findings.

Ketamine increased ACh release from the rat frontal cortex as seen in the rat hippocampus.[1] However, the increase in ACh produced by ketamine 100 mg kg^{-1} showed a biphasic pattern, which was not seen in the hippocampus in our previous study. Although reasons for a biphasic pattern are unknown, a high dose of ketamine may affect ACh release from the frontal cortex via mechanisms different from those after a low dose of ketamine.

Ketamine is known to produce psychostimulant defects such as hyperactivity and memory impairment. It is generally accepted that ketamine is a non-competitive antagonist of NMDA receptors, and there are reports which suggest that ketamine acts at an NMDA recognition site, indicating a role for NMDA receptors in concept learning. NMDA receptors are present in high density in the rat cortex and hippocampus.[6] Hasegawa and colleagues showed that MK-801, another non-competitive antagonist at the NMDA receptor but not an anaesthetic agent, increases ACh release in the rat parietal cortex and that the facilitatory effects of MK-801 on cortical ACh release are blocked by NMDA.[7] This may indicate that the facilitatory effect of ketamine on ACh release from the rat cortex appears to be involved in the antagonism of NMDA receptors, as shown with our previous data for rat hippocampal ACh release.[1]

Our results demonstrated that both ketamine and pentobarbitone produced loss of consciousness, but opposite effects on ACh release from the cortex. This suggests that ACh release in the frontal cortex is concerned with psychomimetic effects other than consciousness. These opposing effects of ketamine and pentobarbitone on cortical ACh release lead us to speculate that the unfavourable psychomimetic actions of ketamine such as bad dreams may be suppressed by simultaneously administered barbitones. Furthermore, several classes of NMDA antagonists, including ketamine, are known to produce morphological damage in neurones in the cerebral cortex and this may be prevented by barbitones, benzodiazepines, or both.[8]

Although the underlying biochemical mechanisms remain to be determined, these opposite effects of ketamine and pentobarbitone on ACh release from the cortex may partly suggest a mechanism underlying the different effects of "dissociative" and "depressant" anaesthetics.

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ABSTRACTS

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All authors have certified that, where appropriate, studies have been conducted with the approval of the relevant Human Ethics Committee or Animal Experimental Review Committee.

Effect of 100% oxygen and 50% nitrous oxide on cerebral autoregulation as assessed by the transient hyperaemic response test

K. J. Girling, G. Cavill*, G. O'Dwyer* and R. P. Mahajan
University Department of Anaesthesia, Queen's Medical Centre, Nottingham

The transient hyperaemic response (THR) of blood flow velocity in the middle cerebral artery after a brief compression of the common carotid artery has been validated as an indicator of cerebral autoregulation.[1] A theoretical model for the quantitative assessment of cerebral autoregulation using the THR has been described by our department.[2] The aim of this study was to determine the effects of breathing 100% oxygen or 50% nitrous oxide in oxygen on cerebral autoregulation.

Eight healthy volunteers were studied in the supine position. Continuous recordings of both cerebral blood flow velocity in the left middle cerebral artery, using transcranial Doppler ultrasonography, and end-tidal carbon dioxide partial pressure at the mouth were established. Each volunteer was subjected to two compressions of the left common carotid artery of 10 s duration while breathing air for baseline measurements. Subsequent measurements were made while breathing 100% oxygen or 50% nitrous oxide in oxygen at fresh gas flow rates of 9–12 litre min^{-1} via a Mapleson A breathing system. Before each compression end-tidal carbon dioxide partial pressure, mean arterial pressure (MAP) and percentages of expired oxygen and nitrous oxide were recorded. Time-averaged mean velocities of the middle cerebral artery pulse waves were analysed as follows: the pulse wave immediately before compression (F1), then immediately after compression (F2) and the first pulse wave after release (F3). Strength of autoregulation (SA) was calculated from the formula (F3/F1)×(P2 /MAP). P2 is the estimated value of the reduced MAP in the middle cerebral artery resulting from carotid artery compression. The value for P2 used in calculating strength of autoregulation is the greater of either that derived from MAP×F2/F1 or 60 mm Hg (assumed lower limit of autoregulation).

Two volunteers could not tolerate 50% nitrous oxide and were excluded from the study. MAP and end-tidal carbon dioxide measurements did not change significantly in any of the subjects.

Breathing 50% nitrous oxide significantly reduced SA compared with air or 100% oxygen ($P<0.01$, paired *t* test). Breathing 100% oxygen resulted in a slight increase in SA compared with air but this was not statistically significant and is not likely to be clinically significant.

In conclusion, the strength of autoregulation was impaired significantly while breathing 50% nitrous oxide.

Table 1 Effect of 100% oxygen and 50% nitrous oxide in oxygen on SA

	Air (n=6)	100% Oxygen oxide (n=6)	50% Nitrous
SA (SD)	0.98 (0.09)	1.09 (0.17)	0.77 (0.11)

Key words
Anaesthetic gases, nitrous oxide. Brain, autoregulation.

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Comparison between reverse Fick and indirect calorimeter measurements of oxygen consumption in patients with fulminant hepatic failure

T. S. Walsh *, P. Hopton* and A. Lee
Department of Anaesthetics and Scottish Liver Transplant Unit, Royal Infirmary, Edinburgh

The reverse Fick method of calculating oxygen consumption ($\dot{V}O_2$) requires multiple clinical measurements, each of which has an associated measurement error. Previous studies in post-cardiac surgery[1] and general intensive care[2] patients have compared this method with indirect calorimeter measurements which are based on analysis of respiratory gases. In these studies the agreement between the methods was poor. In patients with fulminant hepatic failure (FHF) a large cardiac output and small arteriovenous oxygen content difference (AV difference) are typical. This is likely to result in large measurement errors with the reverse Fick method. In this study we compared simultaneous measurements of $\dot{V}O_2$ made with the two techniques in patients with FHF under typical clinical conditions.

Seventeen patients admitted to the intensive care unit with FHF were studied. All patients were sedated, paralysed and their lungs ventilated because of grade III/IV encephalopathy and were resuscitated with fluids and normal adrenaline infusions, as indicated clinically before starting the study. A Deltatrac metabolic monitor (Datex) was used to determine $\dot{V}O_2$ by the gas exchange method. For reverse Fick calculations, cardiac output was measured with the Vigilance system (Baxter). Blood samples from arterial and pulmonary artery catheters were analysed within 5 min of collection with an IL 482 co-oximeter and IL BGE 1400 series analyser. $\dot{V}O_2$ was calculated using the standard formula.

Eleven patients received a standard infusion regime of *N*-acetylcysteine at the start of the study which increases cardiac output in patients with FHF.[3] Six patients received fluids only. Over a 5-h period six pairs of measurements were made in each patient at 0, 30, 60, 120, 180, and 300 min. At each time a 10-min average of cardiac output and gas exchange $\dot{V}O_2$ was recorded.

The mean cardiac index was 5.7 (range 3.4–9.5) litre min^{-1} m^{-2}, Sa_{O_2} 99% (95.4–100%), $S\bar{v}O_2$ 86.3% (75.1–90.5%), AV difference (1.0-2.8) 1.7 ml dl^{-1}. Ninety-eight pairs of measurements were obtained. These were compared with the Bland and Altman method which indicated a negative bias of reverse Fick calculations relative to gas exchange measurements of −41 ml min^{-1} m^{-2} (95% CI −35 to −47). For pooled data the limits of agreement were -101 to $+19$ ml min^{-1} m^{-2}. The mean bias in individual patients ranged from -73 to $+13$ ml min^{-1} m^{-2} and was not related to the mean $\dot{V}O_2$ ($r=0.11$).

The reproducibility of each method was compared by calculating the within-patient standard deviation ($S\omega$) of $\dot{V}O_2$ data using analysis of variance. The ratio of the values of $S\omega$ is then an index of the relative reproducibility of the techniques. For reverse Fick data $S\omega=15$ ml min^{-1} m^{-2}, for gas exchange data $S\omega=7$ ml min^{-1} m^{-2}, ratio 2.2.

Our data indicated that in patients with FHF the agreement between the reverse Fick and gas exchange methods of determining $\dot{V}O_2$ was very poor. The limits of agreement which we calculated were wider than those reported in previous studies in other patient groups. Reverse Fick calculations underestimated gas exchange measurements by an amount which varied widely between patients. The reproducibility of reverse Fick calculations was worse than gas exchange measurements probably because of the small AV difference which typifies these patients. Although neither method was a gold standard our data suggest that the disagreement between the methods is largely attributable to measurement errors in reverse Fick calculations.

Key words

Oxygen, consumption. Measurement techniques, Fick principle. Measurement techniques, calorimetry.

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Desflurane *vs* isoflurane in liver transplantation: a comparison of outcomes

H. A. O'Beirne, Y. Young, J. Thornton* and M. C. Bellamy
Intensive Care Unit, St James's University Hospital, Leeds

During major surgery, splanchnic blood flow is better preserved with desflurane anaesthesia than with isoflurane anaesthesia.[1] We have therefore studied their effects on outcome after liver transplantation in humans.

In a prospective randomized controlled trial, we studied 40 patients undergoing elective liver transplantation. Twenty received desflurane and 20 isoflurane as part of a standard anaesthetic according to our usual technique.[2] Anaesthesia was induced by a high dose opioid-benzodiazepine sequence. Neuromuscular block was produced with atracurium. Patients' lungs were ventilated to normocapnia using oxygen-enriched air, supplemented with 1 MAC of volatile agent. All patients received dopamine 3 μg kg^{-1} min^{-1}. Liver laser Doppler flowmetry was measured after graft re-perfusion, and again immediately before abdominal closure. We measured alanine aminotransferase (ALT), bilirubin, prothrombin time (PT) at 3 and 7 days after surgery. Results are median (range) and were compared using Mann-Whitney *U* test.

Groups were comparable in age, diagnosis, intraoperative blood loss and Child-Pugh score. In the desflurane group, liver blood flow was 67 perfusion units (range 17–219) at re-perfusion, compared with 66 (7–293) in the isoflurane group. At abdominal closure, these values were 70 (13–342), compared with 70 (25–112) perfusion units. There were six serious adverse events in the isoflurane group, but none in the desflurane group ($P=0.02$, Fisher's exact test). Hospital stay for isoflurane patients was 21 (10–47) days compared with 20 (12–57) days in the desflurane group (n.s.).

Table 2 Effect of desflurane and isoflurane on liver function

	Desflurane	Isoflurane	*P*
PT (day 3)	17 (11–27)	17 (13–37)	n.s.
PT (day 7)	14 (12–27)	15 (12–22)	n.s.
ALT (day 3)	239 (52–1787)	534 (34–3170)	0.09
ALT (day 7)	91 (37–294)	176 (49–925)	0.05
BILI (day 3)	63 (16–164)	84 (19–436)	0.07
BILI (day 7)	45 (16–148)	77 (20–318)	0.04

Key words

Anaesthetics volatile, desflurane. Liver, blood flow. Liver, transplantation.

Acknowledgement

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No direct effects of dopexamine on the isolated perfused rat kidney

M. Leuwer, P. Thum*, K. Kirchhoff*, A. Bornscheuer*, W. Seitz*, S. Piepenbrock*, E. Kirchner*
Department of Anaesthesiology, Hannover Medical School and Institute for Peptide Research, Hannover, Germany

Dopexamine, a synthetic catecholamine is thought to increase mesenteric[1] and renal [2] blood flow. It is a specific agonist at type 1 and 2 dopamine receptors and α-adrenergic receptors and has been reported to prevent renal impairment in patients undergoing orthotopic liver transplantation.[3] However, to date there are few reports showing a direct influence of dopexamine on the kidney.[4] Therefore, we investigated the effects of dopexamine in comparison with those of dopamine on renal blood flow (RBF), urine production (UP), glomerular filtration rate (GFR), sodium excretion (U_SV) and fractional sodium reabsorption (FR_s) in an isolated perfused kidney model.[5]

The study was conducted after approval of the local animal protection committee. The right kidney was taken from 40 male Wistar rats. After catheterization of the renal artery and ureter, respectively, the organ was introduced into a closed system and perfused by a substrate-enriched Krebs-Henseleit buffer solution with 5% bovine albumin. Perfusion pressure was 100 mm Hg. After an equilibration period of 20 min and two control periods of 10 min each, dopamine 2.0 mg kg min^{-1} or dopexamine 1.0, 2.5 or 4.0 mg kg min^{-1} were added at random. RBF, UP, GFR, U_sV and FR_s were determined 10, 20, 30 and 40 min after the start of infusion. Urine was collected every 10 min for an 80-min period. Data are presented as mean values (SD). Student's *t* test was used for statistical analysis. $P<0.05$ was considered significant.

Dopamine significantly increased urine production from 77.87 (7.5) to 117.2 (9.7) μl/min x g and absolute sodium excretion from 0.6 (0.1) to 1.2 (0.1) μmol/min x g. Fractional sodium reabsorption significantly decreased from 95.3 (0.4) to 90.7 (0.7) %. Renal blood flow and glomerular filtration rate did not change. In contrast with dopamine none of the dopexamine concentrations tested revealed any significant effects on these parameters.

Dopexamine had no direct effects on the function of the isolated perfused rat kidney.

Key words

Sympathetic nervous system, dopexamine. Rat. Model, rat. Kidney, function.

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Naloxone inhibits gastric emptying but not gastrointestinal transit in the rat

T. Asai, W. W. Mapleson and I. Power
Department of Anaesthetics and Intensive Care Medicine, University of Wales College of Medicine, Cardiff, and Department of Anaesthesia and Pain Management, University of Sydney, RNSH, St Leonards, Australia

Naloxone is generally considered to be a pure antagonist.[1] However, it may produce a hyperalgesic or antinociceptive effect in several species; the effect does not increase systematically with dose, but shows a maximum effect at 1– 3 mg kg^{-1} in rodents when given peripherally.[2 3] We observed that naloxone inhibited gastric emptying in the rat.[4] Therefore, we formally studied the effect of naloxone on gastric emptying and gastrointestinal transit in the rat.

Six to eight Wistar rats (200–250 g) were used for each group. Either saline or naloxone (0.01 – 10 mg kg^{-1}) was injected i.p. at 0 min. At 30 min, radiolabelled saline 1 ml was infused into the stomach. At 1 h, the animal was killed, the gastrointestinal tract was removed and the small intestine was divided into 10 equal segments. Radioactivity in the stomach and each segment of the intestine was counted, and gastric emptying and gastrointestinal transit were calculated. Gastrointestinal transit was assessed using the "geometric centre" ($\Sigma(CiSi)/\Sigma Ci$ where Ci=count in segment Si).[4] The Mann-Whitney *U* test was used to compare gastric emptying or gastrointestinal transit between saline and pooled data for all doses of naloxone. We also calculated 95% confidence limits (CL) for the difference between saline and naloxone in terms of median values for gastric emptying or gastrointestinal transit. A parabola was fitted to the variation of effect with log dose to see if there was any evidence of a peak effect.

Naloxone significantly inhibited gastric emptying ($P<0.001$), but not gastrointestinal transit ($P>0.05$) (table 3). Only gastric emptying showed a significant peak ($P<0.05$) in the dose-response curve – at 0.7 mg kg^{-1}.

Table 3 Effect of naloxone on % gastric emptying (GE%) and gastrointestinal transit (GIT) (median (range) and 95%CL [of median] for difference from 0 dose)

Doses (mg kg^{-1})	GE (%)	95% CL of difference	GIT	95% CL of difference
0	84.3 (82.7, 92.7)	—	5.2 (3.9, 6.2)	—
0.1	66.1 (56.3, 87.0)	[−2.1, 27.3]	4.7 (3.8, 5.5)	[20.7, 1.3]
0.3	75.7 (54.8, 83.5)	[5.4, 27.9]	4.5 (3.8, 5.1)	[0.0, 1.7]
1	59.8 (53.3, 68.9)	[16.0, 31.6]	4.8 (3.3, 5.6)	[−0.5, 1.6]
3	72.4 (55.9, 87.4)	[5.1, 26.8]	4.5 (3.3, 5.2)	[−0.5, 1.8]
10	76,8 (68.5, 82.7)	[2.2, 15.3]	4.6 (3.6, 5.5)	[−0.4, 1.6]

Naloxone significantly inhibited gastric emptying with a peak effect at approximately 1 mg kg^{-1}, but did not significantly inhibit gastrointestinal transit in the rat.

Key words
Gastrointestinal tract, emptying. Pharmacology, naloxone. Antagonists opioid, naloxone.

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Interactive effects of morphine and dexmedetomidine on gastrointestinal transit and gastric emptying in the rat

T. Asai, W. W. Mapleson and I. Power
Department of Anaesthetics and Intensive Care Medicine, University of Wales College of Medicine, Cardiff, and Department of Anaesthesia and Pain Management, University of Sydney, RNSH, St Leonards, Australia

Dexmedetomidine markedly inhibits intestinal transit, but only weakly inhibits gastric emptying; morphine strongly inhibits both.[1] Therefore, we studied the effect of a combination of these two agonists on gastrointestinal transit and gastric emptying in the rat.

Five to eight male Wistar rats (200–250 g) were used for each group. A different combination of the drugs was administered to each group at 0 min; radiolabelled saline 1 ml was infused into the stomach at 30 min, and at 1 h the animal was killed, the gastrointestinal tract was removed and (where relevant) the small intestine was divided into 10 equal segments. Radioactivity in the stomach and in each segment of the intestine was counted; gastric emptying and gastrointestinal transit were calculated.[1] To study the effect on gastrointestinal transit, the two drugs were injected i.p. in a fixed ratio (30: 1) — that of their ED_{50} values [1] — in six doses, each to a different group of rats. These doses (0.062–1.075 mg kg^{-1}) bracketed the ED_{50} predictable on the basis of additivity. The ED_{50} of the mixture, its variance and 95% confidence limits (CL) were determined,[1] and compared with those predicted on the basis of additivity.[2] To study the effect on gastric emptying, another six groups of rats each received a different mixture i.p.: (1) saline and saline; (2) dexmedetomidine 0.01 mg kg^{-1} and saline; (3) morphine 0.22 mg kg^{-1} (ED_{25}) and saline; (4) morphine 0.22 mg kg^{-1} and dexmedetomidine 0.01 mg kg^{-1}; (5) morphine 2.8 mg kg^{-1} (ED_{50}) and saline; (6) morphine 2.8 mg kg^{-1} and dexmedetomidine 0.01 mg kg^{-1}. The Mann-Whitney *U* test was used for comparison of mixtures.

There was a supra-additive interaction between morphine and dexmedetomidine for the inhibitory effect on gastrointestinal transit (fig. 1). Dexmedetomidine 0.01 mg kg^{-1} inhibited gastric emptying ($P<0.01$; CL for difference from saline: (−16%, −5%)), but did not significantly alter the inhibitory effect of morphine on gastric emptying ($P=0.7$ for both doses).

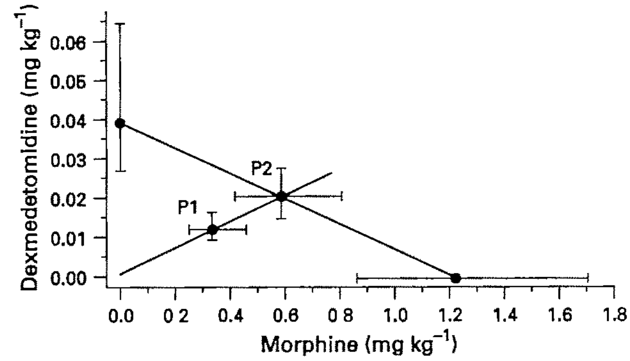

Figure 1 Effect of i.p. morphine and dexmedetomidine on gastrointestinal transit. The observed ED_{50} (0.351 mg kg^{-1}) for the 30:1 mixture (with CL) (point P1) is below the line connecting the ED_{50} values for the two drugs, showing a supra-additive effect; the point P2 is the ED_{50} (0.625 mg kg^{-1}) for the mixture on the basis of additivity; difference in ED_{50} values=0.275, SEM difference=0.114, t =2.4, P=0.02.

In the rat, dexmedetomidine markedly enhanced the inhibitory effect of morphine on gastrointestinal transit, but did not significantly alter the effect of morphine on gastric emptying.

Key words
Gastrointestinal tract, emptying. Interactions, drug, morphine Interactions, drug, dexmedetomidine.

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Comparison of rocuronium and suxamethonium for use during rapid sequence induction of anaesthesia

K. C. McCourt*, L. Salmela*, M. Carroll*, C. M. Kerr*, R. K. .Mirakhur and K. T. Olkkola*
Department of Anaesthetics, The Queen's University of Belfast, Belfast and Department of Anaesthesia, University of Helsinki, Helsinki, Finland

Rocuronium, among the currently available non-depolarizing neuromuscular blocking agents, has the most rapid onset of action, approaching that of suxamethonium when used in doses of 0.6–0.9 mg kg^{-1} and provides intubating conditions comparable with those of suxamethonium at 60 s.[1,2] In this randomized study we compared intubating conditions after suxamethonium or rocuronium during rapid sequence induction.

Three hundred and forty-eight, ASA grade I-IV, patients were enrolled in this two centre study with their written informed consent. The technique of tracheal induction involved preoxygenation for 3 min, administration of fentanyl 1-2 μg kg^{-1} and thiopentone 3-5 mg kg^{-1}, application of cricoid pressure and intubation 60 s after administration of rocuronium 0.6 or 1.0 mg kg^{-1} or suxamethonium 1.0 mg kg^{-1}. Intubating conditions were assessed by an observer blinded to the blocker administered and graded as excellent, good or poor based on standard criteria, the first two grades being considered clinically acceptable.[3] Intubating conditions were analysed statistically using the Mantel-Haenszel chi-square test.

Intubating conditions between the two doses of rocuronium were compared after 63 patients each had been given rocuronium 0.6 and 1.0 mg kg^{-1}, respectively. As the conditions were qualitatively better with the higher dose, further enrolment was made only in the rocuronium 1.0 mg kg^{-1} and suxamethonium groups. In all 318 patients were considered evaluable (61 and 130 for rocuronium 0.6 and 1.0 mg kg^{-1} respectively and 127 for suxamethonium).

The frequency of clinically acceptable intubating conditions was not significantly different between the groups receiving suxamethonium 1.0 mg kg^{-1} and rocuronium 1.0 mg kg^{-1} (P=0.82: table 4). However, excellent conditions were observed more frequently with suxamethonium (P=0.02). We conclude that rocuronium 1.0 mg kg^{-1} can be used during rapid sequence induction of anaesthesia as an alternative to suxamethonium or when the latter is contraindicated. A slightly later intubation time may have to be chosen for attaining uniformly excellent intubating conditions with rocuronium. Careful evaluation of the airway is also important when using rocuronium in view of its longer duration of action.

Table 4 Intubating conditions

Intubating Conditions	Rocuronium 0.6 mg kg^{-1}	Rocuronium 1.0 mg kg^{-1}	Suxamethonium 1.0 mg kg^{-1}
Excellent	17 (28%)	85 (65%)	101 (80%)
Good	29 (47%)	40 (31%)	22 (17%)
Poor	15 (25%)	5 (4%)	4 (3%)

Key words
Neuromuscular blocks, suxamethonium. Neuromuscular block, rocuronium. Intubation, tracheal.

Acknowledgement

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Genetic analysis reveals single recombinants in malignant hyperthermia

J. L. Curran*, W. J. Hall*, P. J. Halsall*, P. M. Hopkins, D. E. Iles*, A. F. Markham*, R. L. Robinson*, S. P. West* and F. R. Ellis
Malignant Hyperthermia Investigation Unit, St James's University Hospital, Leeds

Malignant hyperthermia (MH) is an autosomal dominant genetic disorder manifesting under general anaesthesia. In 1990 a new paradigm in the genetics of MH was established with reports of a locus on chromosome 19q13.2, RYR1.[1,2] However in those studies several of the families described would not be classified as MH if the "gold standard" for diagnosis, the *in vitro* contracture test (IVCT) following the European MH group protocol had been adhered to. Genetic heterogeneity in MH is well established with loci in single families linked to chromosomes 3 and 7 [3,4] and only approximately 60% of families appear to be linked to RYR1. In addition we have recently found linkage to the myotonic dystrophy region (DM) on 19q13.3 in several families (unpublished results), including families in whom linkage to RYR1 has been excluded. We present the results of genetic linkage studies carried out on the largest ever reported series of families to have been screened by the European MH group IVCT protocol. A collection of genetic markers was chosen to see if it would be feasible to move towards DNA based diagnosis.

We have examined 33 large well-characterized MH families with hypervariable microsatellite markers around two of the candidate MH loci (RYR1 and DM). Primers for the markers D19S224, 208, 421, 422, 219, 112 and the CTG repeat in DM were synthesized with a fluorescent tag on the 5′ primer. Polymerase chain reactions (PCR) were performed under standard conditions, and the resultant products analysed on an ABI Genescanner. Results were analysed using Genotyper 1.1 and Cyrillic 2.1 software, followed by statistical analysis with LINKAGE 5.4. Essentially, this involves characterizing the association between inheritance of the disease phenotype (MH susceptibility) and different alleles of the various markers. When a consistent association between particular alleles of markers in the region of a chromosomal locus and the presence of the disease is found, the disease is said to segregate with that locus. If an individual member of a family does not fit the pattern they are termed a recombinant individual. The LINKAGE program provides an objective estimate of likelihood that the disease is truly associated with the locus.

Of the 35 families, 18 clearly segregated with either RYR1 or DM (or with both). Five families failed to show segregation with either of these loci, and are currently being screened with markers for those loci reported previously in single families.[3,4] The remaining 12 families give the most cause for concern, as one member only in each family was found to be recombinant. It is these families in particular that would currently make a move towards DNA based diagnosis of MH extremely unwise.

Key words
Malignant hyperthermia. Genetic factors, hyperthermia.

Acknowledgement

JLC is supported by the British Journal of Anaesthesia.

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Effect of assuming a fixed $(Ca_{O_2}-C\bar{v}_{O_2})$ on shunt calculations

M. Nirmalan*, T. Willard, A. Khan* and P. Nightingale
Intensive Care Unit, South Manchester University Hospitals, Manchester

Measured shunt is considered the most accurate index for quantifying defects in oxygenation. When shunt cannot be measured, the concept of "virtual shunt" using iso-shunt diagrams has been used as a possible surrogate. Oxygen content difference between arterial and mixed venous blood, $(Ca_{O_2}-C\bar{v}_{O_2})$ is assumed to be 5 ml dl^{-1} in the construction of these iso-shunt diagrams. In critically ill patients however, an extraction of 3.5 ml dl^{-1} of oxygen may be a more appropriate value. It has been shown that virtual shunts predicted using $(Ca_{O_2}-C\bar{v}_{O_2})=3.5$ ml dl^{-1} were similar to measured shunts.[1] We have therefore tested the hypothesis that modified iso-shunt curves using $(Ca_{O_2}-C\bar{v}_{O_2})=3.5$ ml.dl^{-1} are likely to be more accurate than the original curves for predicting shunts in critically ill patients.

A total of 211 paired readings of measured and predicted shunt fractions (using two sets of iso-shunt curves) were obtained during a 48-h period from 44 patients. All patients had an indwelling pulmonary artery catheter and arterial cannula, and blood-gas measurements were carried out when indicated clinically. The Bland-Altman statistical test was used to assess the agreement between measured and predicted shunt fractions. Figure 2 shows the comparison between measured shunt and predicted shunt using the new curves.

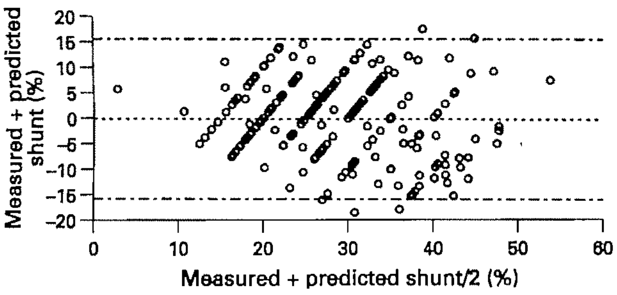

Figure 2 Agreement between measured and predicted shunt using 3.5 ml dl^{-1} for $(Ca_{O_2}-C\bar{v}_{O_2})$

The curves using $(Ca_{O_2}-C\bar{v}_{O_2})=3.5$ ml dl^{-1} over estimated the shunt with a bias of −0.23, whereas the curves using $(Ca_{O_2}-C\bar{v}_{O_2})=5$ ml dl^{-1} under estimated the shunt with a bias of +6.5 (with 95% confidence intervals for bias of 1.1% and limits of agreement of 16%, for both curves). We found a wide range of $(Ca_{O_2}-C\bar{v}_{O_2})$ values (mean 3.62 ml dl^{-1}, range 1.3–7.4 ml dl^{-1}) and wide within-patient variability (mean 1.48 ml dl^{-1}, range 0.6–4.3 ml dl^{-1}). As this lead to wide limits of agreement (16%), these charts cannot be used to accurately quantify defects in oxygenation in the lungs. Our results question the clinical validity of methods that assume a fixed value for $(Ca_{O_2}-C\bar{v}_{O_2})$ in shunt calculations.

Key words
Oxygen, gradients.

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Dose-dependent effects of halothane on contraction of rat ventricular myocytes

L. A. Davies*, S. M. Harrison*, M. R. Boyett* and P. M. Hopkins
Department of Physiology and the Academic Unit of Anaesthesia, University of Leeds, Leeds

Volatile general anaesthetics have been shown to cause depression of contraction of cardiac muscle (for example, Housmans and Murat [1]). We have investigated the negative inotropic effect of a range of halothane concentrations on the contractility of rat ventricular myocytes. Freshly isolated myocytes were superfused with a physiological salt solution at 30°C and contractions elicited by field stimulation at 1 Hz. Contractions were recorded before, during and after 1-min exposure to a solution containing halothane at concentrations in the range 0.01 to 10 mmol litre^{-1}. Halothane was added from 0.5 or 2 mol litre^{-1} stock solutions in DMSO. Figure 3A shows that during the first few seconds after exposure to halothane there was marked potentiation of contractions, followed by a pronounced and maintained negative inotropic effect. When halothane was washed off there was further transient depression of contractions which then recovered to control values. The initial potentiation of contraction was more marked with higher halothane concentrations. Figure 3B illustrates the dose-dependency of the maintained decrease in contraction (expressed as a percentage of control) induced by halothane. These data were fitted with a Hill curve with a K_d of 0.5 mmol litre^{-1} and a Hill coefficient of 1.2. These results show a dose-dependent inhibitory action of halothane on cardiac contractility at a range of halothane concentrations encompassing those seen clinically (0.05–0.69 mmol litre^{-1})[2]

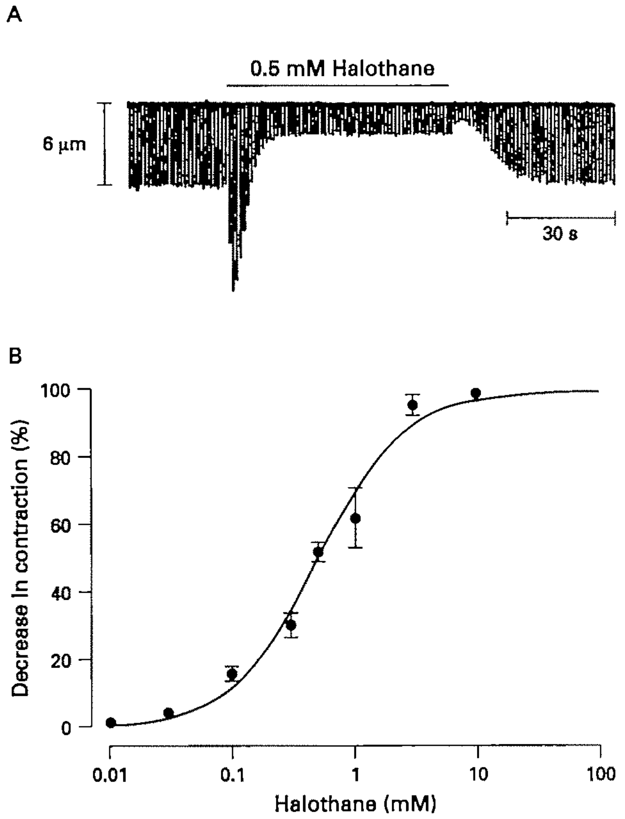

Figure 3 (A) Effect of 0.5 mmol litre^{-1} halothane (applied during the period shown by the bar) on contraction (shortening of the cell during each contraction shown) of a rat ventricular myocyte. (B) Dose-dependence of the negative inotropic effect of halothane. Means (SEMS) ($n=6$–40).

Key words
Anaesthetics volatile, halothane. Heart myocytes. Rat

Acknowledgement

This work was supported by a *British Journal of Anaesthesia* project grant.

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Ultrasonographic measurement of gastric emptying in volunteers: assessment of technique and effect of low-dose dopamine

D. R. Goldhill, S. A. White*, N. O. Owen* and W. Hately*
The Anaesthetics Unit and Radiology Department, The Royal London Hospital, London

The objectives of this pilot study were to determine the variability in gastric emptying measured ultrasonographically and the effect of low-dose dopamine. Dopamine at 8 μg kg min^{-1} decreased gastric emptying in volunteers [1] and dopamine 2–4 μg kg min^{-1} appeared to decrease gastric emptying in ICU patients.[2]

The cross-sectional area of the gastric antrum was measured ultrasonographically in the sitting position in two sagittal planes, at the level of the aorta and the inferior vena cava (IVC) [3] in six healthy, starved volunteers. Antral area was calculated from the maximal anteroposterior (AP) and longitudinal diameters (L) by the formula AP=L π/4. To estimate gastric emptying a baseline measurement was made and subjects ingested 500 ml of sterile water at a known temperature. Repeated measurements of antral area were made at intervals of 2.5 min for 25 min (control). Using a double-blind, randomized design subjects then received an infusion of saline or dopamine 3 μg kg min^{-1}. After 2 h of infusion measurements were repeated. Each subject received both saline and dopamine with an interval of at least 1 week between studies.

At each time the average of the antral area at the aorta and IVC was calculated. The area increased after drinking water then decreased over 25 min. The decrease was not consistent from one measurement to the next because of peristalsis. To smooth the data a running average over three times was calculated. The time for the maximum area to decrease by half was estimated as a measure of gastric emptying. Comparisons were made between controls and between control and saline and control and dopamine using paired *t* tests. No significant differences were found.

There is considerable day-to-day and time-related variability in gastric emptying measured ultrasonographically. A 2 h dopamine infusion at 3 μg kg min^{-1} did not significantly slow gastric emptying measured with this method.

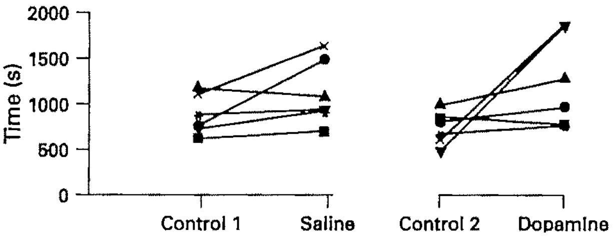

Figure 4 Time for antral area to fall to 50% of maximum (three point moving average).

Key words
Gastrointestinal tract, emptying. Measurement techniques, ultrasound. Heart, dopamine.

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Modelling the photographic "restricted window" to derive "true glottic view"

P. Groom*, J. Talbot*, and P. Charters
Department of Anaesthesia, Aintree Hospitals, Liverpool, and Department of Medical Illustration, Aintree Hospitals, Liverpool

The perceived view of the glottis results from panning multiple "eyelines" to construct a composite panoramic image, the "true glottic view". In contrast, a still camera takes a single eyeline snapshot resulting in a partial view of the glottis, the "restricted window".[1] The aim of this study was to determine if it was theoretically possible, for a given laryngoscope blade, to use a restricted window photograph to derive the true glottic view. Line diagrams would be used to predict true glottic view and a restricted window and these measurements would be checked against photographic equivalents in a physical model.

An accurate acetate template for the shape of a Macintosh 4 laryngoscope blade was produced by progressive correction using computer graphics. This was superimposed on the upper incisors and glottis (fig. 5A) to determine the true glottic view. The restricted view was a parallel beam with lower border from incisors to the posterior glottis and upper border tangential to the lower lingual surface of the blade (fig. 5B). The photographic restricted window and true glottic view were determined using two equivalent eyelines in a physical model with a ruled scale (the glottis), the pointed edge of a transverse longitudinal bar (the incisors) and the same blade from which the template was constructed. Three variables were investigated: depth of blade insertion (90 to 130 mm), glottic depth (15 to 30 mm) and blade angulation (0 to 20 degrees). Angulation of the blade describes its rotation about the upper incisor.

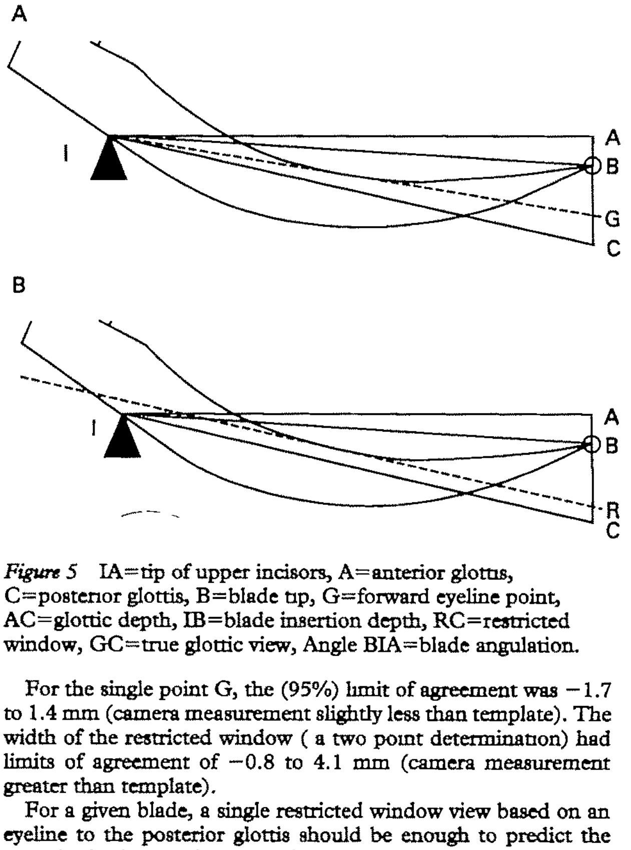

Figure 5 IA=tip of upper incisors, A=anterior glottis, C=posterior glottis, B=blade tip, G=forward eyeline point, AC=glottic depth, IB=blade insertion depth, RC=restricted window, GC=true glottic view, Angle BIA=blade angulation.

For the single point G, the (95%) limit of agreement was −1.7 to 1.4 mm (camera measurement slightly less than template). The width of the restricted window (a two point determination) had limits of agreement of −0.8 to 4.1 mm (camera measurement greater than template).

For a given blade, a single restricted window view based on an eyeline to the posterior glottis should be enough to predict the true glottic view (and also glottic depth). Apart from blade shape, the only other data needed are depth of blade insertion and blade angle, both of which are readily accessible.

Keywords
Anaesthetic techniques, laryngoscopy. Model, simulation.

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Epiglottis modelling in a computer simulation of difficult laryngoscopy

M. Hawkins* and P. Charters
Department of Anaesthesia, Aintree Hospitals, Liverpool

A mathematical model for osseous factors in difficult laryngoscopy has been reported.[1] This recently formed the basis for a two dimensional computer simulation which depended on the position of the laryngoscope blade, and definable osseous constraints (e.g. degree of mandibular recession).[2] The eventual goal is an accurate three dimensional simulation including movements of soft-tissue structures. Contact of the laryngoscope blade tip with the hyoid is important for controlling elevation of the epiglottis.[3] It could be hypothesized that control of the epiglottis is lost proportionately as difficulty increases, that is the epiglottis gradually tilts posteriorly. Alternatively, if contact between the blade tip and hyoid is critical, loss of control may occur with minor degrees of difficulty, that is tending to let the epiglottis flop posteriorly, obstructing the view of the laryngeal inlet. The aim of this study was to determine epiglottis behaviour in this regard, to facilitate modelling in the simulation.

Lateral x-ray images of 25 volunteers undergoing laryngoscopy under topical anaesthesia were reviewed. Sixteen had been referred to the department, having been difficult in the past. The other nine were normal controls. On each image the following points were marked: I=tip of incisor; A=anterior glottis; P=posterior glottis; B=blade tip; E=tip of epiglottis. Angles were used for the analysis, as they are size independent. For the computer algorithms, it is convenient to model a theoretical straight-line blade. (This allows different blade shapes to be added later, but it does assume the tip is positioned similarly for each.) Of most interest is the relation between angles BIA and EAI. PIA and EIA were also measured as the glottis is obscured from view when PIA is less than EIA.

The plot for BIA (degrees) *vs* EAI (degs) appeared linear (see fig. 6).

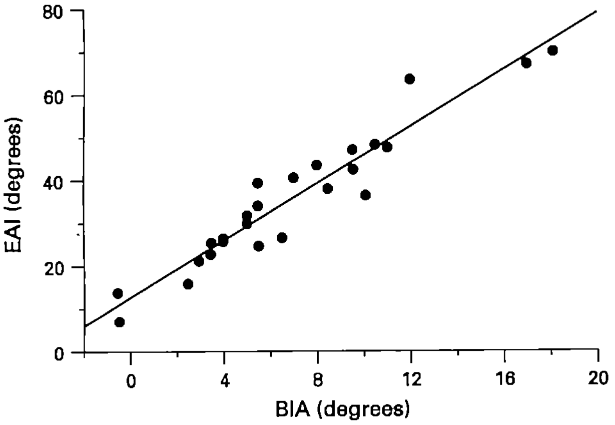

Figure 6 Relationship between EAI and BIA.

Equation for line,

$$\text{EAI (degrees)} = \frac{3.32\times\text{BIA}}{\text{(degrees)}+12.59}$$

Correlation coefficient, $r=0.955$

PIA range was 9.5–18 degrees (median=11.5, interquartile range=10.5–13.5 degrees). With increasing difficulty the view of the glottis was obscured and BIA=7 (degrees) appeared to be a cut-off point where PIA=EIA.

The results suggest that loss of control of the epiglottis is progressive.

Key words
Anaesthetic techniques, laryngoscopy. Model, computer simulation.

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Body posture during simulated tracheal intubation

A. J. Matthews*, C. J. H. Johnson* and N. W. Goodman
Department of Anaesthetics, Southmead Hospital, Bristol

Textbooks have pictures[1] of the best position of head and laryngoscope blade during tracheal intubation, but we could find no information on the best posture for the person performing the intubation. During our teaching of medical students, we thought that students tended to crouch more over patients, and to peer more closely. This is a report of a formal comparison of the posture of novices and skilled people during intubation.

We filmed (Canon E70 camcorder) intubation of a Laerdal intubation manikin on a standard fixed height operating theatre trolley during two intubations by each subject. For the first we filmed left side-on, and for the second end-on. We asked the subjects to tell us when the tracheal tube was in the larynx. For some subjects, we took a close-up of the hand-grip on the laryngoscope. Filming was done by one investigator (CJ) in as near standard positions as possible, using a tripod.

Three video frames were captured at the "moment" of intubation (Macintosh Performa 5300, SimpleText) for each subject: side-on, end-on, grip. Another investigator (N.G.) anonymised and coded the images (GraphicConvertor v2.5), before the third investigator (T.M.) analysed them from colour hard copy (Epson StylusColor 500) or screen images (NIH Image v1.52). Elbow angle and distance from subject's nose to manikin's chin were the two primary variables. We also measured the angle at the shoulder (nose-shoulder-elbow). Nose-chin was converted to true distance. The results are presented as median and interquartile range and compared using the Mann-Whitney *U* test (StatView SE v 1.4) (table 5).

We studied 17 skilled (eight consultants, nine trainees) and 15 novices (nine medical students, four surgical trainees, two trainee operating department personnel).

Elbow angle ($P<0.01$) and nose-chin distance ($P=0.01$) were smaller for the novices; shoulder angles were not significantly different ($P=0.19$). There were too many different hand-grips for any objective measures, but the novices were more likely to hold the laryngoscope further from the hinge. Novices were also more likely to have their forearm below the horizontal; four novices had their elbow on the trolley.

Table 5 Angles at elbow and shoulder, and distance from subject's nose to manikin's chin, during tracheal intubation of an intubation dummy. Medians (interquartile range)

	Elbow angle	Nose-chin (cm)	Shoulder angle
Skilled	108°	43	43°
	(99–120)	(41–56)	(38–47)
Novices	92°	37	39°
	(88–102)	(25–41)	(33–42)

We conclude that there are systematic differences in the way skilled people and novices stand during tracheal intubation. Undoubtedly intubation was more difficult for the novices, and we do not know whether crouching was because of difficulty, or whether the difficulty was caused by crouching. It may be that skilled people are more likely to crouch for a difficult intubation. However, for simple mechanical reasons keeping the arm more straight encourages lifting of the laryngoscope and bending the elbow encourages levering of the laryngoscope.

Key words
Intubation tracheal, training.

Reference

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Bolus doses of alfentanil prevent the increase in Pa amplitude associated with intubation in a dose-dependent manner

G. Skinner*, R. M. Sharpe*, C. Shannon*, C. Thornton, C. J. Doré and M. D. Brunner
Department of Anaesthesia, Northwick Park Hospital, Middlesex

The amplitude of the early cortical wave, Pa, of the auditory evoked response (AER) decreases with increasing hypnosis[1] and increases after a stimulus, for example intubation[2], indicating arousal. Alfentanil infusions block the increase in Pa amplitude associated with intubation in a dose-dependent manner.[3] This study investigated the effect of bolus administration of alfentanil on Pa amplitude in response to intubation.

This study was approved by the local Ethics Committee. Forty-five unpremedicated ASA I or II patients, aged 18-65 yr, gave written informed consent. Anaesthesia was induced with propofol 2 mg kg^{-1} and vecuronium 0.1 mg kg^{-1} and the lungs ventilated for 15 min with 50% nitrous oxide in oxygen to 0.6 MAC end-expiratory isoflurane using a laryngeal mask airway (LMA). Normocapnia was maintained. They were then allocated randomly into three equal groups. Group A received saline (control), group B, alfentanil 15 $\mu g\ kg^{-1}$ and group C, alfentanil 50 $\mu g\ kg^{-1}$. The bolus doses were given 1 min before the LMA was removed and the patients' tracheas were intubated; this reflects the distribution time for alfentanil from plasma to brain. The early cortical AER in response to a 6 Hz click stimulus was recorded from forehead and mastoid electrodes throughout. AER data corresponding to 2.6 min before administration of alfentanil or saline and after intubation were analysed and compared.

The change in Pa amplitude after intubation was determined for each group. One-way analysis of variance was performed after $\log_{10}$ transforming the data and the group means were tested for linearity.

After intubation (fig. 7), Pa amplitude increased in the control group A by 60% (+10 to +130, 95% CI) and decreased in the alfentanil groups; group B by 11% (−38 to +29, 95% CI) and group C by 26% (−49 to +7, 95% CI). There were significant ($P<0.005$) linear trends in the three group means for Pa amplitude.

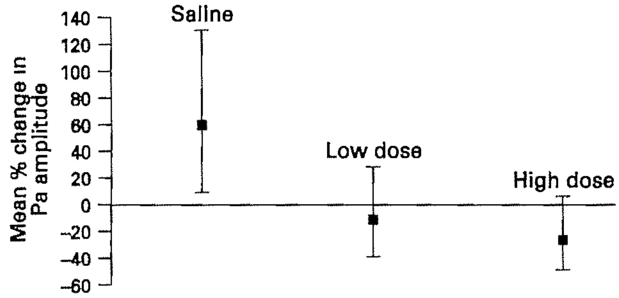

Figure 7 Mean percentage change in Pa amplitude after intubation (95% CI) in the three groups.

We have demonstrated that the increase in Pa amplitude associated with tracheal intubation was blocked by bolus administration of alfentanil, 60 s before intubation.

Key words
Analgesics opioid, alfentanil. Intubation tracheal. Monitoring, evoked potentials.

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Preoperative education reduces side effects when patient-controlled analgesia is used

M. J. Griffin, L. Brennan and A. J. McShane
Department of Anaesthesia and Intensive Care, St Vincent's Hospital, Dublin

Patient-controlled anaesthesia (PCA) is a relatively new means of analgesia administration which has many theoretical advantages. However, a significant number of patients using PCA obtain inadequate pain relief and have significant symptoms ascribed to PCA resulting in premature termination and poor results. Anxiety and poor coping skills are predictors of postoperative pain[1] and may be reduced by education. This study determined the effect of detailed preoperative education on postoperative PCA use, pain, patient satisfaction, side effect profile and antiemetic use.

Eighty-five patients undergoing major procedures were allocated randomly to group A (special tuition) or group B (no special tuition). Written consent was obtained from group A patients ($n=42$) who received detailed preoperative education including standardized in depth explanation of PCA and a visual demonstration. Group B patients ($n=43$) consented to postoperative pain and satisfaction score assessment, a chart review and received non-standardized information from their anaesthetist at the preoperative visit. Visual analogue scale (VAS) assessment of pain and satisfaction, morphine consumption, side effects, antiemetic use and rescue analgesia requirement were recorded in recovery, and at 6 h, 24 h and 48 h. Statistical analysis of morphine consumption, pain and satisfaction scores was performed using the Mann-Whitney *U* test. Side effects, antiemetic and rescue analgesia requirements were compared with the chi-square test.

Both groups had similar morphine consumption, pain and satisfaction scores at all stages. Pain scores were low and satisfaction scores were high throughout in both groups. Group A demonstrated significantly greater antiemetic use at 6 h and 24 h ($P<0.05$) and significantly less nausea and vomiting at 24 h ($P<0.05$). Twelve group A patients and 22 group B patients complained of nausea by 24 h. At 6 h, 12 group A patients and five group B patients had requested antiemetic medication. At 24 h, 15 group A patients and eight group B patients had requested an antiemetic.

PCA results in excellent analgesia and a high degree of satisfaction irrespective of the intensity of preoperative tuition. Preoperative PCA tuition seems to result in more sensitive and efficient use of antiemetic medication and an improved side effect profile. Warning patients in advance of these side effects and how to deal with them may result in more efficient and effective use of PCA.

Key words:
Analgesia, patient-controlled. Pain, postoperative.

Acknowledgement

We acknowledge grant support from the Health Research Board.

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Assessment of neuromuscular monitoring by intensive care nurses: comparison of the TOF-watch and tactile assessment

R. Greer*, A. J. Pearson and N. J. N. Harper
Intensive Care Unit, Manchester Royal Infirmary, Manchester

Neuromuscular monitoring of ICU patients is important because the action of these drugs varies greatly in this population. Tactile assessment of train-of-four (TOF) is used commonly to assess the degree of block . Acceleromyography uses the principle that the acceleration of a muscle is proportional to the force of contraction (Newton's second law). The TOF-watch is a new, compact device for monitoring neuromuscular block by means of acceleromyography.

In patients with steady state neuromuscular block our aims were: (1) to investigate the ability of ICU nurses to assess the number of TOF twitches, and (2) to investigate the ability of nurses to detect tactile TOF fade and assess the TOF ratio.

We investigated 20 stable, sedated, adult patients receiving an infusion of atracurium. The nurse in charge of the patient (nurse A) made a tactile TOF assessment and then made a TOF-watch measurement. Four subsequent tactile assessments were made immediately by different nurses who were blinded to the TOF-watch result. At the same time as the tactile assessment, nurse A made a TOF-watch assessment. One minute elapsed between measurements.

Nurses incorrectly assessed the number of TOF twitches in approximately 50% of estimates (fig. 8).

A Bland and Altman plot demonstrated bias such that the nurses tended to overestimate the TOF ratio.

Nurses tend to underestimate the degree of block when assessing the TOF ratio in the ICU.

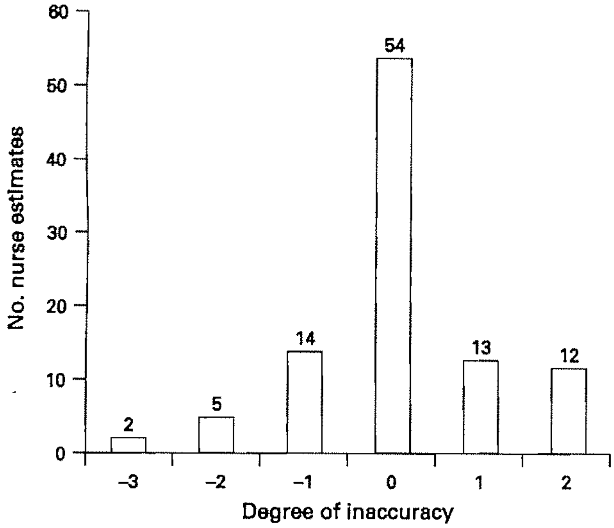

Figure 8 Degree of inaccuracy for nurses estimating TOF twitch count.

Key words
Monitoring, neuromuscular function. Intensive care. Neuromuscular block, measurement of response.

Effect of music on the psychomotor performance of anaesthetists

C. R. E. Hawksworth*, P. Sivalingham* and A. J. Asbury
Department of Anaesthesia, Western Infirmary, Glasgow

Playing music in the operating theatre is commonpace in the U K. A recent survey showed most anaesthetists feel this is generally not distracting.[1] Self-chosen music has a beneficial effect on the mental performance of surgeons.[2] We undertook this study to determine if music affected anaesthetists' psychomotor performance.

Twelve anaesthetists took part in this study. Subjects performed two tests from the PsychE computerized psychomotor evaluation programme developed in this department. After practice runs with both tests, subjects wore padded headphones and were asked to perform each pair of tests four times while listening to Pachelbel's Canon in D, their own self-chosen music, "white noise", or silence. The order in which the music was played was determined by a 4X4 orthogonal Latin square design to counter cross-over effects. The first test was the numeric vigilance test. Three-digit numbers were presented on the computer screen at a rate of 100 per minute. Each number differed randomly from the previous number by one digit. Eight per cent of these numbers were duplicates of the previous number. Subjects were asked to identify these duplicates by pressing the keyboard spacebar when they occurred. Correct responses, missed duplicates and superfluous responses were recorded.

The second test was a dual test — tracking and simple reaction time. The primary task was to use the computer mouse to follow a randomly moving target on the screen with a cursor. The percentage of time the cursor was on target was recorded. The secondary task was to identify the random appearance of a yellow symbol on the screen by pressing the spacebar. The time taken to press the spacebar was recorded.

We were unable to demonstrate a difference in the scores obtained under any of the music conditions using Friedman's test for non-independent repeated measures (table 6). This implies that anaesthetists' psychomotor performance under laboratory conditions is not affected by music. However, this may not necessarily apply in theatre conditions.

Key words
Anaesthetist, performance.

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Table 6 Scores in psychomotor tests for each type of music. (Medians with 95% confidence limits.) Friedman's test indicated no difference in medians at 95% significance level

	Silence	White noise	Pachelbel	Self-chosen
Vigilance: No. hits	12.7 (11–14)	12.8 (11–13)	12.7 (11–13)	12.6 (11–13)
Dual test: Reaction time (ms)	415.0 (373–478)	430.0 (398–481)	420.0 (404–473)	427.0 (390–458)
Dual test: % time on target	85.3 (65.0–91.7)	85.5 (66.0–93.0)	84.8 (58.9–89.5)	84.0 (66.3–89.7)

POSTER PRESENTATIONS

Buscopan does not improve pain after laparoscopic sterilization

C. M. Wilson*, N. Lillywhite*, S. Wiltshire* and P. Mills*
Department of Anaesthesia, Ipswich Hospital, Ipswich

Laparoscopic sterilization is performed frequently as a day-case procedure. Smooth muscle spasm induced by clips placed on the Fallopian tubes may be an important cause of postoperative pain. A study from this institution has shown that glycopyrronium (anticholinergic and antispasmodic agent) improves pain scores after laparoscopic sterilization.[1] Buscopan is used to relieve smooth muscle spasm in radiological investigation.[2] We investigated the effect of i.v. buscopan on pain scores, analgesia requirements and the incidence of nausea and vomiting after laparoscopic sterilization.

Forty-five patients were studied in a prospective randomized study. Patients were premedicated with diclofenac 100 mg p.r. Anaesthesia was induced with midazolam 2 mg, fentanyl 100 µg, droperidol 0.625 mg and a sleep dose of propofol. Anaesthesia was then maintained with oxygen, nitrous oxide and 1–2% enflurane via a laryngeal mask airway. Patients were then randomized to receive either placebo or buscopan 20 mg i.v. before the start of surgery. Postoperative analgesics were administered at patient request; co-dydramol two tablets orally or morphine 10 mg i.m. Prochlorperazine 12.5 mg was given as required for nausea. Pain and sedation scores were assessed by a blinded observer on admission to recovery and at 1, 2 and 3 h after operation. Incidence of nausea and vomiting and any analgesic or antiemetic drugs given were also recorded. Data were analysed with parametric and non-parametric tests as appropriate, with $P<0.05$ taken as statistically significant.

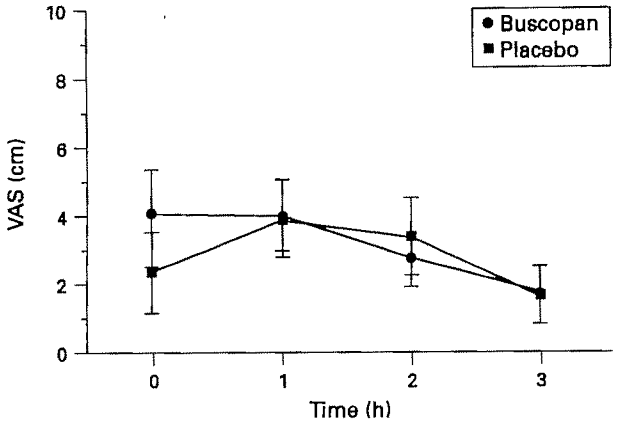

Figure 9 Pain scores (mean (95%) CI) at 0, 1, 2 and 3 h after operation.

The main findings are shown in figure 9. There were no significant differences in pain scores, sedation or nausea and vomiting between the two groups.

We conclude that buscopan 20 mg i.v. did not improve pain after laparoscopic sterilization.

Key words
Pain, postoperative. Surgery, gynaecological. Pharmacology, buscopan.

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Halothane decreases K^+ evoked glutamate release from rat cerebrocortical slices

B. Nicol*, D. J. Rowbotham and D. G. Lambert
University Department of Anaesthesia, Leicester Royal Infirmary, Leicester

We have shown previously that ketamine and thiopentone decreased K^+ evoked glutamate release from rat cerebrocortical slices.[1] As there are conflicting reports of the effects of halothane on evoked glutamate release[2 3] we have examined the effects of this agent on K^+ evoked release from rat cerebrocortical slices.

Cerebrocortical slices (350 µm×350 µm) were cut from Wistar rats. The slices were suspended in oxygenated (95% oxygen/5% carbon dioxide) Krebs buffer, pH 7.4, for 40 min before loading into a perfusion chamber.[1] The slices were perfused at 1 ml min^{-1} for 60 min. A 2 min pulse of 46 mmol $litre^{-1}$ K^+ (Na^+ adjusted) was then applied (S_1). A second pulse of K^+ (S_2) was applied after a further 40 min of perfusion. Slices were exposed to halothane (mean 85 SEM 6), 222 (4) and 395 (16) µmol $litre^{-1}$, equivalent to 0.24, 0.61 and 1.09 rat MAC) immediately after S_1 until the end of the experiment via a precalibrated Fluotec 3 vaporizer. Aqueous halothane concentrations stated were measured by gas chromatography. Glutamate concentrations were measured fluorimetrically.[1] Area under the stimulation curves (S_1 and S_2) was estimated and the S_2/S_1 ratio calculated. The effect of halothane on the control S_2/S_1 ratio was analysed by Wilcoxon rank sum test and considered significant when $P<0.05$. All data are mean (SEM). K^+ produced monophasic release of glutamate during S_1 and S_2 (fig. 10) yielding an S_2/S_1 ratio of 1.06 (0.12) (n=12) under control conditions. The S_2/S_1 ratio was reduced by 34 (7)% (n=5, $P<0.05$), 48 (8)% (n=6, $P<0.05$) and 63 (7)% (fig. 10, n=6, $P<0.05$) with 0.24, 0.61 and 1.09 rat MAC halothane, respectively.

Collectively these data support an inhibitory effect of halothane on K^+ evoked glutamate release. The mechanism(s) of this inhibitory effect is currently under investigation.

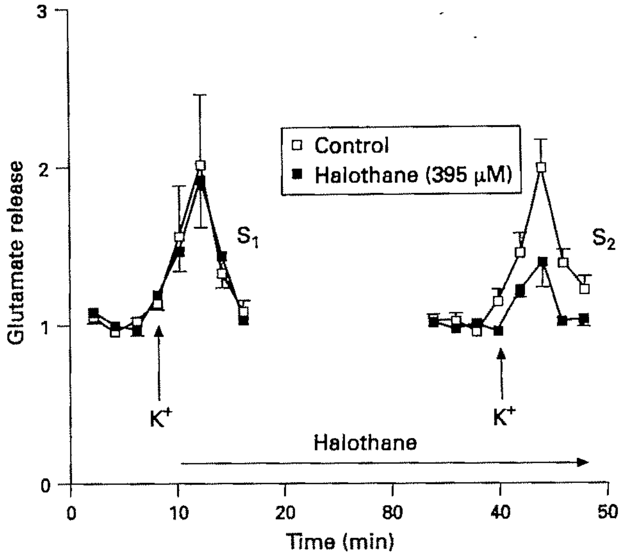

Figure 10 Halothane (1.09 rat MAC) inhibited K^+ evoked glutamate release. Glutamate release is expressed relative to the mean of the first three basal samples.

Key words
Anaesthetics volatile, halothane. Brain, anaesthesia, molecular effects. Model, rat. Rat

Acknowledgement

Financial support from Trent Regional Health Authority is gratefully acknowledged.

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Preliminary survey into clinical attitudes to computer based decision support systems

P. C. W. Beatty
University Department of Anaesthesia, Manchester Royal Infirmary, Manchester

Computer based decision support systems promise to be able to offer clinical staff new alarm systems, better detection of critical incidents and on-line advice on treatment strategy. However, such systems will not be used unless their designs meet the preferences, prejudices and expectations of the clinical staff. To investigate these clinical attitudes, we conducted a preliminary survey of medical and non-medical clinical staff in operating theatres, intensive care units and recovery at the Manchester Royal Infirmary.

A Likert style survey form was circulated to 81 anaesthetists (30 consultants, 51 trainees), 100 ICU nurses and 26 other members of staff including recovery nurses and ODA. Six questions with 12 choices concerning attitudes were asked. A separate section asked questions on profession, grade, experience, age and sex. Subjects were also asked to grade their access to/use of computers and computer literacy. Non-responders to the questionnaire were not followed up in this preliminary study so as to avoid potential bias of answers by giving extra information to subjects. The mean rate of return was 26.6%. The questionnaire included notes that were intended to give staff unfamiliar with the concept of such a computer based decision support system sufficient background information. All responses were pooled and the relative agreement/disagreement to choices within questions were examined using Friedman rank coefficients. Differences between groups were investigated using Mann-Whitney *U* testing, with the responses divided between medical and non-medical staff and alternatively those specializing in general anaesthetics or ICU. Finally, responses to choices were grouped by underlying "issue" using factor analysis.

All responders favoured characteristics in systems that advise or guide rather than control. Consistently, the non-medical group were more prepared to give control to computer systems than were their medical colleagues. This bias reached statistical significance in the case of nine choices in three questions ($P<0.05$). There were no consistent differences between the ICU and general anaesthetics groups, although four choices in three questions did show significant differences. Responses indicated that staff welcomed the idea of detailed advice on treatment off-line, preferably through flow diagrams, but wanted on-line advice limited to alarms, which should be more sophisticated. The opinion that should be used for such advice should be drawn from as wide a group of experts as possible. Extra physiological measurements would be welcomed. Responders wanted the systems to compensate for failures of vigilance.

The attitudes of responding clinical staff are consistent with other studies on operator confidence in computer systems.[1] As the rate of return was low, this preliminary study must be validated by repeating the questionnaire with follow up on a wider basis.

Key words
Anaesthesia, audit. Computers.

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Effects of ketamine on cAMP formation in Chinese hamster ovary cells expressing recombinant opioid receptors

K. Hirota, B. L. Appadu, D. K. Grandy*, L. A. Devi* and D. G. Lambert
University Department of Anaesthesia, Leicester Royal Infirmary, Leicester, Vollum Institute, Oregon, USA and Department of Pharmacology, New York University Medical Center, USA

Ketamine has been reported to interact with opioid receptors and to produce analgesia.[1] Opioid receptor agonists inhibit adenylyl cyclase thereby reducing cAMP formation.[2] We have reported that ketamine interacts stereoselectively with opioid receptors with a rank order potency of $\kappa>\mu>\delta$.[3] However, these studies provide limited information as to the nature of the interaction. To consider this question we have examined the effects of ketamine on cAMP formation in Chinese hamster ovary (CHO) cells expressing recombinant κ, μ an δ (CHOκ, μ and δ) receptors, respectively.

CHOκ (passage 5–8), CHOμ (passage 13–16) and CHOδ (passage 7–10) cells were maintained in supplemented Hams F12 medium. All experiments were performed using whole cells at 37°C in 0.3 ml of Krebs/HEPES buffer, pH 7.4 containing isobutylmethylxanthine 1 mmol litre^{-1}. The effects of ketamine were examined on forskolin (10 μmol litre^{-1}) stimulated and spiradoline, [D-ala^2, MePhe^4,Gly(ol)^5]enkephalin (DAMGO) and [D-Pen^{2,5}]enkephalin (DPDPE) inhibition of forskolin stimulated cAMP formation in all cell types. All data are mean (SEM) ($n \geq 4$).

Spiradoline 2.0 nmol litre^{-1}, DAMGO 100 nmol litre^{-1} and DPDPE 5.0 nmol litre^{-1} inhibited forskolin stimulated cAMP formation in CHOκ, CHOμ and CHOδ cells by 28.8 (3.1), 36.8 (2.4) and 41.1 (1.9)% respectively. Ketamine produced a dose-dependent naloxone (10 μmol litre^{-1} insensitive inhibition of cAMP formation in all cells, including untransfected CHO cells (table 7). Co-incubation of ketamine (1 mmol litre^{-1}) and subtype selective agonists was neither additive nor synergistic.

These data demonstrate that ketamine inhibited adenylyl cyclase but that this inhibition was not mediated by the opioid receptor. Despite our previously reported interaction of ketamine with opioid receptors other non-opioid mechanism(s) are likely to underlie ketamine analgesia.

Table 7 Log molar concentration of ketamine producing 50% inhibition (pIC_{50}) of cAMP formation in CHOκ, μ and δ cells Mean value (mmol litre^{-1}) quoted in parentheses. (CHOwt cells are untransfected)

	CHOκ	CHOμ	CHOδ	CHOwt
pIC_{50}	2.576±0.050 (2.65)	2.684±0.051 (2.07)	2.694±0.086 (2.02)	2.696±0.054 (2.01)

Key words
Receptors, opioid. Anaesthetics i.v., ketamine. Hamster.

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Effect of sevoflurane on spontaneous sympathetic activity and baroreflexes in rabbits

D. Ma*, S. M. Sapsed-Byrne*, M K. Chakrabarti and J. G. Whitwam
Department of Anaesthesia, Royal Postgraduate Medical School, Hammersmith Hospital, London

Previous studies, in humans and animals, showed that while sevoflurane was not associated with major significant changes in heart rate (HR) and sympathetic nerve activity,[1 2] it caused a concentration-dependent reduction in arterial pressure.[3] We have studied the potential role of baroreflexes on its effects.

Sixteen New Zealand White rabbits were anaesthetized (methohexitone bolus 10–15 mg.kg^{-1} and 1% α-chloralose 15–20 mg kg^{-1} h^{-1} i.v.), paralysed (suxamethonnium 10 mg i.v. every 20–30 min) and their lungs ventilated mechanically. Blood-gas tensions and pH*a* and oesophageal temperature were kept within normal limits. Fascicles of renal sympathetic nerves were exposed, desheathed, cut distally, immersed in a mineral oil pool and mounted on electrodes for recording renal sympathetic nerve activity (RSNA). The preparations were divided randomly into three groups: in group 1 ($n=7$) sevoflurane was administered at 1%, 2%, 3% and 4% end-tidal concentration each for 20 min; group 2 ($n=4$) received an infusion of sodium nitroprusside (SNP) for 60 min to lower mean arterial pressure (MAP) to 30–40 mm Hg; group 3 ($n=5$) was used to observe baroreflex sensitivity by using arterial depressor and pressor tests with bolus injections of either SNP 2, 4, 8 and 16 μg kg^{-1}) or phenyleprine 0.5, 1, 2 and 4 μg kg^{-1} before and after 1% and 2% sevoflurane administration. Baroreflex sensitivity was evaluated by deriving the relation between ΔHR, ΔRSNA and ΔMAP in response to SNP-induced hypotension and phenyleprine-induced hypertension, and also by calculating the ratio of the maximum changes in HR and RSNA to the maximum changes in MAP (ΔHR/ΔMAP; ΔRSNA/ΔMAP) produced by the largest dose of 16 μg kg^{-1} of SNP and 4 μg kg^{-1} of phenyleprine, respectively.

At similar mean MAP values between 40 and 80 mm Hg, SNP caused statistically significant increases in HR from 249 beats min^{-1} to 292 beats min^{-1} ($P<0.05$) and RSNA by 150% ($P<0.05$); sevoflurane up to 3% did not change RSNA which decreased to 63% of control values at 4% ($P<0.05$), without any significant change in mean HR from a control value of 246 beats min^{-1}. Baroreflex sensitivity was attenuated by sevoflurane expressed as relationship curves between ΔHR , ΔRSNA and ΔMAP, and also expressed as the ratio of ΔHR/ΔMAP and ΔRSNA/ΔMAP.

Sevoflurane depresses the baroreflex sensitivity. However, depressed baroreflexes continue to compensate for the depressant effect of sevoflurane on sympathetic activity up to 3% and on cardiomotor activity up to 4% concentration.

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Key words

Anaesthetics volatile, sevoflurane. Receptors, baroceptors. Rabbit.

British Journal of Anaesthesia 1997; 79: 143–146

CORRESPONDENCE

Absence of memory for intraoperative information

Sir,—I wish to comment on the article by Russell and Wang on absence of memory for intraoperative information during surgery under adequate general anaesthesia.[1]

Their study seemed to have been motivated by their belief that the brain can only process information during anaesthesia if anaesthesia is inadequate enough to result in the patient being conscious. Using the isolated forearm technique (IFT), they showed that there was no evidence for explicit recall, or implicit memory changes in patients, for times at which these patients were unresponsive to verbal command.

I would agree that changes in implicit memory are more likely to occur at times when the anaesthetized patient is responsive to verbal command, but their assumption that an observed response when using the IFT automatically indicates a state of consciousness is, I believe, not warranted.

As they themselves quoted, with some general anaesthetic techniques more than 70% of patients may be capable of responding to commands during surgery (using IFT), with no postoperative explicit recall of intraoperative events. It is still not necessarily the case however, that the patient was conscious, even if postoperative changes in implicit memory are demonstrated in these patients. All this implies is that the brain has processed information in some way and created a response.

The authors seem to believe that IFT acts as a reliable "consciousness monitor" or indicator of "adequate" anaesthesia, but they disregard the possibility that responses observed while using this technique might also reflect pre-conscious information processing. In other words, whereas patients might respond appropriately, they might still not be conscious.

The major fault with this study is that in attempting to disprove the notion of pre-conscious information processing, they make use of a clinical tool (IFT) which, much of the time, may in fact measure exactly what they wish to disprove.

Until when, and if, it is demonstrated that this type of anaesthesia results in significant psychological morbidity, there is no reason to suppose that it is not "adequate".

M. B. HOOPER
Department of Anaesthesia
Townsville General Hospital
Townsville, Queensland
Australia

1. Russell IF, Wang M. Absence of memory for intraoperative information during surgery under adequate general anaesthesia. *British Journal of Anaesthesia* 1997; 78: 3–9.

Sir,—Dr Hooper speculates on our motives for conducting this study.[1] The background is the voluminous literature apparently demonstrating implicit learning during general anaesthesia.[2–4] Typically, these studies involve the use of neuromuscular blocking agents and absence of systematic intraoperative monitoring of levels of consciousness. Given the poor relationship between intraoperative cognitive function and postoperative explicit recall,[5] it is quite possible that in many of these studies intraoperative information was presented to patients who were wakeful. Our study demonstrated that when level of consciousness is controlled such that there is insufficient higher cortical function to allow response to command, verbal learning (whether explicit or implicit) is precluded.

Dr Hooper's use of the terms "conscious" and "unconscious" is misleading, because it assumes two discrete states. The evidence generated by interest in memory and awareness during anaesthesia over the past decade[2–4] demonstrates that we have a continuum, which can be delineated in terms of various experimental paradigms.

Dr Hooper's letter also implies the common misconception that absence of postoperative recall is synonymous with intraoperative oblivion, and therefore "adequate anaesthesia". Readers who have clinical experience of patients with dense amnesic states such as Korsakoff's psychosis need no persuading of the mistake in this assumption. Memory function in such patients is irreversibly impaired such that memory of moment-to-moment experience is not maintained beyond a few minutes. However, it would be wrong to characterize them as having impairment of *consciousness*: all other cognitive functions may be normal, they are commonly alert and have a clear sensorium. The relevance of this for anaesthetists is that many drugs used in general anaesthesia have precisely these types of effects on memory function, albeit in a reversible manner.[6]

We are unclear as to what Dr Hooper means by "pre-conscious processing". Normally this term refers to *perceptual* processes which occur without the involvement of higher cortical function. We are certainly not attempting to dispute the existence of such processes. However, it is incorrect to suggest that specific motor responding to a verbal command is purely a function of pre-conscious processing. Response to command, particularly if that command involves conditional clauses such as "if you are in pain, squeeze your fingers twice" clearly involves operation of higher cortical centres. It seems that Dr Hooper is attempting to use the term "pre-conscious processing" as a semantic device with which to dismiss the significance of high levels of intraoperative cognitive processing.

M. WANG
Clinical Psychology Unit
University of Hull
Hull
I. F. RUSSELL
Department of Anaesthesia
Hull Royal Infirmary
Hull

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Sevoflurane or halothane for paediatric endoscopy

Sir,—We were interested in the conclusion of Meretoja and co-workers in their article comparing halothane with sevoflurane for paediatric endoscopic procedures.[1] We have recently undertaken an audit of sevoflurane, as a new drug, in this anaesthetic department and found that in a study of 344 adults and children, only two patients complained of nausea or vomited in the recovery area after administration of sevoflurane. An analysis of the patients in our audit by the ages used in the study of Meretoja and colleagues showed that of 17 patients aged 3–11 months, 92 patients aged 1–5 yr and 14 patients aged 6–15 yr who received sevoflurane for induction and maintenance of anaesthesia, only two patients in the middle age group vomited. A total of 20 patients aged 3–11 months, 243 patients aged 1–5 yr and 66 patients aged 5–16 yr (with 15 adult patients) also received sevoflurane for maintenance of anaesthesia with no additional patients suffering nausea and vomiting. All paediatric patients are kept in the recovery area for a minimum of 30 min and those patients treated in the day surgery facility were observed for a minimum of 1 h in recovery after anaesthesia and for a minimum of an additional 1 h before discharge.

The observation that a relatively short administration of sevoflurane may confer antiemetic properties, similar to those of propofol,[2] in the postoperative period has been confirmed by other authors and our audit.[3-5] A recent study comparing propofol and sevoflurane found that the incidence of nausea and vomiting was higher in patients receiving sevoflurane than in those receiving propofol, but this finding was not present in earlier work from this group.[6 7]

We also noted an emergence phenomenon similar to that reported by Johannesson, Floren and Lindahl; 19 of 329 children in our audit were observed to be "distressed", "restless" or "agitated" in the recovery area.[3] There were no long-term adverse sequelae.

We would support the conclusion of Merotoja's group that further studies are indicated to confirm (and quantify) any antiemetic properties of this new volatile agent.[1]

A. Plowman
J Barson
J. Clarke
S. Bolsin
Department of Anaesthesia
The Geelong Hospital
Geelong, Victoria
Australia

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Spinal anaesthesia: effect of the site of injection on the spread of analgesia

Sir,—I read the article by Veering and co-workers[1] with much interest. In their study they examined the effect of the site of injection on analgesia levels after spinal injection of 0.5% hyperbaric bupivacaine solution. The patients received 3 ml of 0.5% hyperbaric bupivacaine for spinal anaesthesia either at the L3–4 (group 1) or L4–5 (group 2) interspace. The highest analgesia levels in their study did not differ between groups.

In my opinion, the results of their study are not as disappointing as the authors claim. Admittedly, the results of their study showed that the difference in the level of maximal spread of analgesia between the two groups was not statistically significant. However, if we examine the results of their study more closely, we note an interesting difference, in group 1 (L3–4), six of 15 patients developed the highest level of analgesia to the fifth thoracic dermatome or higher, compared with only two of 15 patients in group 2 (L4–5). Although this may be a biased approach, it is nevertheless a high sensory level of spinal anaesthesia that should be avoided, as patients are at increased risk of developing hypotension. Therefore, it is probable that the small statistically insignificant difference in maximum decrease in SAP occurred in this group of patients.

On the other hand, one patient in group 2 developed the highest level of analgesia to the T12 dermatome, which was probably insufficient for blocking the pain caused by bladder distension during surgery.

It is a pity that the authors did not include an additional higher level of subarachnoid puncture in their study. There may have been a difference in the sensory level of analgesia between injection of the local anaesthetic solution at the L4–5 interspace compared with injection at the L2–3 interspace.

In my opinion, when we perform spinal anaesthesia we should try to choose a higher approach to the subarachnoid space (preferably L2–3) and give less local anaesthetic. This could result in better control of spread of analgesia in decreasing the number of patients with too high and too low analgesic levels after spinal anaesthesia.

M. Kamenik
Department of Anaesthesiology, Intensive Care and
Pain Management
Maribor Teaching Hospital,
Ljubljanska, Maribor, Slovenia

1. Veering BTh, Riet PM, Burm AGL, Stienstra R, Van Kleef JW. Spinal anaesthesia with 0.5% hyperbaric bupivacaine in elderly patients: effect of site of injection on spread of analgesia. *British Journal of Anaesthesia* 1996; 77· 343–346.

Sir,—Thank you for the opportunity to respond to the comments of Dr Kamenik on our article.[1] As noted, the highest levels of analgesia after injection via the L3–4 and L4–5 interspaces did not differ. In his comments Dr Kamenik draws attention to the fact that six of 15 patients who received injection via the L3–4 interspace had the highest analgesia levels extending to T5 or higher compared with only two of 15 patients who received the injection via the L4–5 interspace. Furthermore, Dr Kamenik relates the higher incidence of high thoracic analgesia levels to the slightly larger, although not statistically significant, decrease in systolic arterial pressure in patients who received the injection via the L3–4 interspace.

The question which must be addressed in this respect is whether or not we might have missed a true difference in the levels of analgesia associated with injection via the L3–4 and L4–5 interspaces. As noted in the article, the study was based on a power analysis of earlier observations, and aimed at an 80% probability of detecting a difference of two segments, which we considered clinically relevant. This includes a 20% probability of missing a true difference of two segments, which is generally considered acceptable from a statistical point of view. Of course, the probability of missing a true difference of one segment is considerably greater. In this respect the comments of Dr Kamenik may be justified. However, as his comments are based on isolated observations, these are highly speculative and should be tested prospectively, possibly by a study aimed at the number of patients reaching analgesia levels in the high thoracic region. The same is true for his comment on the single patient in whom the analgesia level was restricted to T12.

We did not include a group of patients receiving injection via the L2–3 interspace because an earlier study revealed no difference in analgesia levels after injection via the L2–3 and L3–4 interspaces.[2] In addition, the injection sites were selected on anatomical considerations, as described previously and discussed in our article. Briefly, hyperbaric solutions, under the influence of gravity, migrate preferentially to the lower levels of the subarachnoid space (i.e. below L3 to T4 in the lumbosacral concavity and above L3 to L4 in the thoracic concavity).[3 4] As such it is expected that injection of a hyperbaric solution via the L2–3 interspace with the patient in the sitting position during injection and until 2 min thereafter, followed by horizontal supine positioning, would result in higher analgesia levels than injection via the L4–5 interspace.

Overall, inter-individual variation in analgesia levels after subarachnoid injection of hyperbaric bupivacaine solutions is impressive, especially in elderly patients. Any modifications in the spinal procedure that could reduce this variability and prevent excessive cephalad spread of the local anaesthetic solutions, and thereby result in a more predictable and safer spinal block, would be welcome. The suggestion of Dr Kamenik to reduce the dose of local anaesthetic may deserve investigation.

B. Th Veering
P. M. Ter Riet
A. G. L. Burm
R. Stienstra
J. W. Van Kleef
Department of Anaesthesiology
Leiden University Medical Centre
Leiden, The Netherlands

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Cuff deflation for easier weaning from ventilation

Sir,—We read the editorial by Shneerson[1] with great interest and agree that much work needs to be done to assess the relative importance of each of the new approaches during the weaning process.

Shneerson stated that cuff deflation is probably the single most underrated and important step in improving upper airway function and should have a central place in the preparatory phase of weaning. The reason cited is that deflation of the cuff improves the co-ordination of the laryngeal and pharyngeal muscles by re-instating the respiratory function of the larynx and by allowing patients to speak.

The above explanation is logical; however, another immediate advantage of deflating the cuff is reduced work of breathing, allowing easier weaning. During quiet breathing, intrapleural pressure at the base of the lungs varies between −2.5 mm Hg and −6 mm Hg.[2] However, if an adult breathes through a size 9.0 mm internal diameter (id) tracheal tube, peak intrapleural pressure developed during normal inspiration is approximately −15 mm Hg,[3] indicative of increased work load of breathing. A size 8.0 or 9.0 mm id tracheostomy tube should also produce changes of similar magnitude. Although these changes seem modest, in patients with weaning problems they could be clinically important. Even a small reduction in work load of breathing could be crucial in determining the outcome in such patients.

Deflation of the cuff allows the patient to breathe both through the lumen and also from around the tube. This leads immediately to a significant decrease in the resistance and work load of breathing. The fact that patients are able to phonate is evidence of the higher resistance offered by the tracheostomy tube compared with the rest of the upper airway. Speech would not be possible if the resistance of the tracheostomy tube was much less than that offered by the upper airway, as this would allow the air to escape through the tracheostomy tube, taking the path of least resistance.

Sleep deprivation in intensive care during the recovery phase is widespread and deserves further attention. Attempts should be made to establish a normal sleep–wake cycle. Generally patients in intensive care units are receiving constant rate infusions of sedatives and analgesics. Perhaps administration of sedatives to follow the circadian rhythm may help, so that during the night patients are well sedated and during the day, almost awake. Whether patients would benefit from such a strategy is open to question and needs further investigation.

P. Bapat
Department of Anaesthetics
Charing Cross Hospital
London
C. Verghese
Department of Anaesthetics
Royal Berkshire Hospital
Reading

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Sir,—I thank Drs Bapat and Verghese for their comments. I agree that cuff deflation reduces the work of breathing and can enable patients to breathe spontaneously at an earlier stage in the weaning process. This benefit of cuff deflation is distinct from its use in improving upper airway function and is only of value when the patient is not attached to the ventilator. In contrast, upper airway coordination can be improved both when the patient is breathing spontaneously and while receiving ventilatory support. Cuff deflation can be used to achieve this, even before withdrawal of ventilatory support is attempted or between initial trials of this. These two benefits of cuff deflation, reduction of work of breathing and improvement in upper airway function, are therefore complementary and assist the weaning process in different ways.

J. Shneerson
Respiratory Support and Sleep Centre
Papworth Hospital
Cambridge

Prophylaxis against deep vein thrombosis

Sir,—Wheatley and Veitch in their editorial on recent advances in prophylaxis against deep vein thrombosis stated that women receiving the combined oral contraceptive pill (OCP) should discontinue it 6 weeks before elective surgery.[1] While it is accepted that combined OCP users are at increased risk of venous thromboembolism, in the absence of other risk factors there is insufficient evidence to support a policy of routinely stopping the combined OCP before surgery.[2] A burden of responsibility is put on the person advocating stopping the combined OCP to arrange suitable alternative contraception. Failure to do so risks unwanted pregnancy, the effects of anaesthesia and surgery on an undiagnosed pregnancy and termination of pregnancy with its physical and emotional sequelae. The Royal College of Obstetricians and Gynaecologists Working Party report on thromboprophylaxis made three recommendations.[3]

(1) Patients receiving combined oral contraception should have a risk assessment profile performed, as with any patient undergoing gynaecological surgery.

(2) The combined oral contraceptive need not be ceased nor thromboprophylaxis commenced in women undergoing uncomplicated minor and intermediate procedures.

(3) Patients receiving combined oral contraception who are assessed as moderate risk should receive one of a variety of prophylactic measures. Whether it is necessary to cease oral contraception before surgery is unclear, but if this is done, adequate counselling regarding pregnancy risk or alternative contraception (e.g. progestogen only pill) should be provided. The situation with regard to the patient's additional risk factors should be considered on an individual basis.

Wheatley and Veitch also stated that hormone replacement therapy (HRT) has not been shown to increase the risk of thromboembolic disease. This is not accurate. Three recent studies have shown an increased risk of venous thromboembolism in users of HRT.[4–6] The risk of a blood clot increases from 1:10 000 per year in those not receiving HRT to 3:10 000 per year in those who are, so the effect of replacement treatment seems to be small. Assessing risk based on age and other risk factors still pertains.

J. R. Allsop
Department of Obstetrics and Gynaecology
Ipswich Hospital NHS Trust
Ipswich

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Sir,—Dr Allsop is correct in highlighting an area of continuing controversy regarding thromboembolic prophylaxis for women taking the oral contraceptive pill (OCP). The report of the Royal College of Obstetricians and Gynaecologists Working Party[1] does not consider taking the OCP to be an independent risk factor for thromboembolic disease in patients undergoing surgery, but in combination with pre-existing risk factors it admits that there is uncertainty as to whether the OCP should be stopped before surgery. In contrast, the European Consensus Statement[2] regarded any woman receiving the OCP as being at an increased risk and therefore warranted either cessation of this medication 4–6 weeks before surgery or some type of prophylaxis. Obviously any woman who ceases to take the OCP must be advised to use adequate alternative contraception if she is to avoid the unquantified risk of unwanted/undiagnosed pregnancy and termination.

The three recent studies showing an increased risk of thromboembolic disease in women receiving hormone replacement therapy (HRT) were all published in the same edition of the *Lancet* after this editorial was written, and represent some of the first evidence that HRT may be associated with such a risk.

T. J. WHEATLEY
Department of Surgery
Leicester General Hospital
Leicester

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Intraocular pressure and suxamethonium

Sir,—After reading the case report of the use of rocuronium in a pregnant patient with an open eye injury by Gaiser and Seem,[1] I feel that it is necessary to comment on their recommendations concerning the avoidance of suxamethonium.

As in many situations there is a balance of risks to be sought before choosing any particular anaesthetic technique. In this case the authors decided that the risks of damage to the injured eye in using suxamethonium outweighed the risks of using rocuronium in a pregnant patient with a potential full stomach and a known increased incidence of difficult intubation.[2] But is this the correct balance of risks? Rocuronium removes the safety net that suxamethonium has of potentially wearing off, should intubation be difficult or impossible, and what is the evidence that suxamethonium causes problems in open eye injury? It is true that suxamethonium causes an increase in intraocular pressure (IOP) of 10 mm Hg,[3] but not using suxamethonium does not imply that increases in IOP are avoided as laryngoscopy alone may cause an increase of 10–15 mm Hg[4 5] and coughing can lead to an increase in IOP of 40 mm Hg.[6] Blinking increases IOP by 5 mm Hg[7] and forceful eyelid closure may cause an increase of up to 70 mm Hg,[8] events likely to have occurred in any person who has suffered a severe eye injury.

In addition, as long ago as 1957[9] thiopentone was shown to abolish the increase in IOP associated with suxamethonium, and Edmondson and colleagues[10] demonstrated in 1988 that there were no significant increases in IOP compared with baseline values when suxamethonium and thiopentone were used as part of a rapid sequence induction and intubation.

More recently, and more significantly, Moreno, Kloess and Carlson[11] using an anterior and posterior trauma model in the cat eye found that there were no cases of vitreous extrusion in 38 separate administrations of suxamethonium. From this they concluded that suxamethonium, when indicated, should be considered in patients with suspected or known open globes.

Have there been cases of vitreous extrusion after suxamethonium reported in the literature? Very few can be found. In 1957 Lincoff, Breinin and DeVoe[9] reported several cases (by personal communication) of prompt expulsion of vitreous when suxamethonium was used to try and forestall impending vitreous extrusion; an unfair situation in which to put all the blame on suxamethonium. The only other report of expulsion of intraocular contents after suxamethonium that I could find was a letter by Rich and colleagues in 1986,[12] but no anaesthetic details were given. This contrasts sharply with the combined 900 cases of penetrating eye injury reported by Libonati, Leahy and Ellison[13] and Donlon[14] where the use of suxamethonium caused no additional damage to the eye.

In conclusion, until we have a non-depolarizing neuromuscular blocking agent with the same potency and short duration of action as suxamethonium, it will always have a place in the balance of risks for a patient with an open eye injury.

L. EDMONDSON
Anaesthetic Department
Wansbeck General Hospital
Ashington, Northumberland

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British Journal of Anaesthesia 1997; 79: 147

BOOK REVIEWS

Handbook of Critical Care, 2nd Edn. R. R. KIRBY, R. W. TAYLOR AND J. M. CIVETTA (editors). Published by Lippincott-Raven, Philadelphia. Pp. 940; indexed; illustrated.

This is the second edition of this manual of critical care. In essence it contains the reference material from the third edition of the textbook *Critical Care* by the same editors, without the background scientific material.

There is a huge amount of information in this book, but extensive use of subheadings, lists, diagrams, highlighted text and panels make it easy to find the relevant information quickly.

The book is divided loosely into two halves covering surgical and medical intensive care, and then subdivided into 11 major sections and a total of 65 chapters. Each chapter contains details of diagnosis and treatment, expected laboratory findings and clinical information, and also a considerable amount on related practical procedures. Many of the descriptions of procedures are accompanied by excellent line drawings, and in general the illustrations in the book are excellent. A set of appendices give useful tables and data.

This is, of course, an American book and so contains American drug names and non-SI units, and the resuscitation guidelines follow the American Heart Association algorithms. However, this should not pose a practical problem in understanding or using the information in the book. A chapter summarizing the treatment of poisons would have been helpful, although most of the information is available elsewhere in the book.

In summary, this is an excellent pocket size handbook containing a wealth of information on all aspects of intensive care. It is the type of book which should be available in the intensive care unit to help all grades of practitioners with day to day problems. I would urge you to buy one for yourself.

J. D. Young

Practical Obstetric Anesthesia. D. M. DEWAN AND D. D. HOOD (editors). Published by WB Saunders, Philadelphia. Pp. 385; indexed; illustrated. Price £39.00.

Writing a practical guide to an area of practice as controversial as obstetric anaesthesia must be a daunting undertaking. This book is aimed at "obstetric anaesthesia care providers", and covers both the relevant background and actual delivery of care. Therefore, it fits into the gap between purely practical guides and Chestnut's comprehensive *Obstetric Anesthesia, Principles and Practice*.

The first chapters cover background material, including a review of anaesthetic-related maternal morbidity and mortality, relevant physiology and pharmacology, and a discussion of fetal and maternal monitoring. The emphasis throughout is on the practical relevance of the information presented.

Next are sections on analgesia for labour and anaesthesia for Caesarean section. There is much that is controversial in this field, but the authors present consistently safe and effective practice and cover most of the relevant techniques. There is much good advice, with emphasis on early resiting of extradurals rather than struggling with poor blocks. The UK reader, however, will search in vain for any reference to the use of 0.5% hyperbaric bupivacaine for spinal anaesthesia, because of the North American emphasis of the book.

The later chapters are a series of well chosen topics related to the "complicated" obstetric patient. These chapters are mostly excellent, and include relevant background and practical advice on management throughout. Chapters on anaesthesia for non-birth-related surgery in pregnancy, postoperative analgesia, resuscitation and medico-legal aspects conclude the book.

The multi-author text has been well edited, and there is good cohesion between chapters with minimal repetition. The list of "10 practical points" at the end of each chapter works surprisingly well. Each chapter is followed by a list of references, which are generally useful and up to date. The standard of presentation is excellent, with clear layout and good print. The many useful tables and diagrams make it easy to find information.

It is written entirely by North American practitioners, and therefore to the UK reader there are the usual unfamiliar drug names, and much information on drugs which are not used widely in the UK (e.g. 2-chloroprocaine, amylocaine and sufentanil). Perhaps more important are the many real differences in practice between the two cultures. For example, although the use of Entonox is acknowledged as still being common in the UK, the use of inhalation analgesia in labour is dismissed as "impractical in many new units", and in another chapter is dismissed altogether because of its "potential to ... obtund airway reflexes". Similarly, TENS is omitted from the chapter on analgesia in labour, although hypnosis and acupuncture are mentioned. (Interestingly both TENS and Entonox are mentioned as possibilities for the woman with AIDS in labour.) The North American experience with bupivacaine is emphasized throughout, with constant references to its increased toxicity in labour.

Despite this, there is much that is good in this book. I would recommend that the delivery suite keep a copy. It will be well used.

P. Rasey

Cambridge Textbook of Accident and Emergency Medicine. D. SKINNER, A. SWANN, R. PEYTON AND C. ROBERTS (editors). Published by Cambridge University Press, Cambridge. Pp. 1271; indexed; illustrated. Price £120.00.

The book has 1271 pages, is indexed and, although text-based, has many appropriate illustrations where required.

Accident and emergency is a new specialty, in the past borrowing information from other specialties where required. The only substantive texts have been American. This truly excellent book is the first of real stature to appear in accident and emergency and is extremely welcome.

It is notable that there are many authors, both from accident and emergency, and other specialties and, indeed, from other countries, showing the diverse nature of the specialty from major trauma to dermatology, pre-hospital to non-accidental injury, airway to envenomation.

The book is divided into three sections: general principles, trauma, medical, surgical and obstetric emergencies. The trauma section follows very closely ATLS principles and priorities, other sections dealing with children follow PALS and cardiac sections follow ALS principles and philosophy. Indeed, even the structure of the chapters (introduction, dialogue and closure) follows the educational principles of these three major training courses. The last section is set out in a problem-orientated, rather than diagnosis-orientated way, which is the system used in accident and emergency.

I feel this is a must for all trainees in accident and emergency, particularly of registrar and above standard. I think it ought to be available in all accident and emergency departments as a reference for SHOs and other visiting specialist junior doctors.

It would also form a good reference for many other specialties in training, particularly paediatric, anaesthetic and surgical, as it provides up to date techniques and management protocols which are sometimes not covered fully in other texts. The reference sections are very topical.

Although accident and emergency is a small specialty, it touches many others in hospitals, in addition to pre-hospital practice; this textbook forms an excellent reference for those involved and is highly recommended.

D. Quinton

Papers for publication and all editorial communications should be addressed to:
Dr J. M. Hunter,
Editor-in-Chief, *British Journal of Anaesthesia*,
University Department of Anaesthesia,
Royal Liverpool University Hospital,
The Duncan Building,
Daulby Street,
Liverpool L69 3GA.
Tel./Fax: 0151 706 4005

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"I would have everie man write what he knowes and no more."—MONTAIGNE

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EDITORIAL

Resuscitation

In 1942 Geoffrey Organe,[1] later Professor Sir Geoffrey Organe, addressed the Section of Anaesthetics of the Royal Society of Medicine on "resuscitation". His presentation focused on cardiac arrests occurring in association with anaesthesia and surgery and his assessment of the attempts at resuscitation. In 1942 monitoring of cardiac rhythm, oxygenation and ventilation, which we take for granted today, was not available; electrical defibrillation and external cardiac massage had not been considered; i.v. fluid was considered hazardous in most cases, but blood transfusion was recognized as treatment for overt haemorrhage. Adrenaline (*epinephrine* see below) was used, but was thought on occasion to cause ventricular fibrillation. Organe showed remarkable foresight in his suggested routine for resuscitation. This included clearing of the airway and artificial ventilation with oxygen, the pros and cons of tracheal intubation, direct stimulation of the heart by transthoracic puncture of the right atrium (although no mention is made of injecting drugs by this route), direct cardiac massage by laparotomy and, if necessary, opening the chest through the diaphragm, and finally the use of drugs. Injection of adrenaline transthoracically into the left ventricle is advocated as "a measure of desperation" and the use of procaine if the "surgeon's hand confirms ventricular fibrillation" during cardiac massage. Lignocaine (*lidocaine* see below) had yet to be developed in 1942. Organe concluded "if a satisfactory circulation is not established within four to five minutes, permanent damage to the brain is likely to occur, leading to death at a later period". Some 55 years on the urgency of restoring the circulation accompanied by adequate ventilation is still centre stage.

This year has seen major changes in resuscitation concepts and it is very appropriate that the *British Journal of Anaesthesia* should take "resuscitation" as a title for a postgraduate issue. Anaesthetists have been one of the driving forces in promoting a rational approach to resuscitation, starting with the confined area of cardiac arrest in the operating theatre, to the current trend of teaching basic and advanced life support to all health professionals, involvement in intensive care medicine and trauma, in addition to special situations. The reviews in this issue cover all of these aspects and provide the reader with a current view. We should not forget the major contributions of other specialties to resuscitation and its international nature. This is illustrated by our authors in this issue and the membership of organizations such as the Resuscitation Council of the United Kingdom, the European Resuscitation Council (ERC) and the International Liaison Committee on Resuscitation (ILCOR). These groups[2] are currently upgrading their guidelines, all of which are referred to in this issue.

Resuscitation is not performed by most anaesthetists on a regular basis. However, there is a perception that we are the lead specialty in this area. Part 3 of the FRCA contained as part of its examination process a station on resuscitation in the objectively structured clinical examination (OSCE). This required candidates to demonstrate, using a manikin, basic life support and pattern recognition of cardiac arrythmias. Despite wide publicity, it was clear that some candidates were unaware of any of the algorithms displayed on the walls of most hospitals. The OSCE has now been moved to the new Primary FRCA and it would not be betraying any secret to point out that the resuscitation station is still there. *BJA* is sometimes accused of not being clinical enough in its content. This issue gets to the heart of a part of clinical practice which all anaesthetists, regardless of their interests, be they trainees or consultants, should be confident that they could do correctly if required. Do you know where the defibrillator and resuscitation drugs are in your operating theatres, intensive care unit and other acute care settings? Do you know how to use the defibrillator? In a recent coroner's court in the UK some 15 health professionals (including some anaesthetists) had to own up to the fact that none knew how to operate the defibrillator provided for them at a cardiac arrest.

Many of the reviews show protocols to be followed in the various aspects of resuscitation. These have been devised by consensus and represent best thinking at the time they are published. None is written in stone and the various resuscitation councils would be the first to acknowledge that they will be subject to change. Randomized clinical studies of resuscitation protocols have obvious ethical and practical difficulties. Nevertheless, uniform reporting in resuscitation is part of the way forward and one review details current thinking in this area. Some of our senior colleagues do not find protocol compliance easy; they believe that their personal experience outweighs any protocol. However, a recent article[3] in this journal showed that when faced with a simulated critical incident, anaesthetists' recollections were at variance with what actually occurred. Therefore, it might be better for all of us to contribute to the consensus rather than to a nihilistic approach. The latter is much easier and sometimes makes entertaining reading in non-peer reviewed publications, but in the real clinical world it is hard to defend a colleague who knows nothing of protocols and has clearly not done anything else based "on their experience" to resuscitate a patient.

Resuscitation by its nature deals with emergencies and often involves staff not always familiar with all aspects of a patient's condition and treatment. We are now quite good in many situations at immediate restoration of the circulation, as advocated by Organe, but of course the patient may not eventually survive. Should we have started on resuscitation in the first place without all the relevant information? The review on ethical aspects of resuscitation explores this difficult area. It is not now fashionable to assume that doctors take the Hippocratic oath on qualification, but the principle expressed in "I will use treatment to help the sick according to my ability and judgement, but I will never use it to injure or wrong them" is surely one to which all doctors subscribe.

Finally, what's in a name? Around the world the names adrenaline, noradrenaline and lignocaine often follow what might be called their original nomenclature as written here; but increasingly as drug manufacture has become international, epinephrine for adrenaline, norepinephrine for noradrenaline and lidocaine for lignocaine have become more common. As this postgraduate issue illustrates, much of resuscitation is protocol driven to accommodate the wide range of health personnel involved. Obviously any confusion over the names of key resuscitation drugs is undesirable. The solution rests with an attempted international agreement between all national authorities that epinephrine, norepinephrine and lidocaine should be the recommended names and that they would be mandatory for all publications after April 1998. The reviews in this issue of the journal were recruited before this agreement was sought and the current journal style is for the original names of the drugs. In the UK the authority on names of drugs is the Medicines Control Agency. To date it has yet to agree to the changes. *BJA* will, of course, abide by any decision of the Medicines Control Agency and readers will see a change of style, if necessary, in future issues.

P. J. F. BASKETT
Frenchay Hospital
Bristol BS16 1LE
L. STRUNIN
Editor of Educational Reviews
British Journal of Anaesthesia

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Basic life support

A. J. HANDLEY

This review introduces the new guidelines for basic life support for use in the UK, approved by the Resuscitation Council (UK), and based on the work of the International Liaison Committee on Resuscitation. Some of the background reasoning behind the development of these guidelines is discussed.

Basic life support

The term basic life support (BLS) refers to maintaining an airway and supporting breathing and the circulation. It comprises the following elements: initial assessment, airway maintenance, expired air ventilation (rescue breathing; mouth-to-mouth ventilation) and chest compression. When all are combined the term cardiopulmonary resuscitation (CPR) is used. BLS implies that no equipment is used; when a simple airway or face mask for mouth-to-mask resuscitation is used, this is defined as "basic life support with airway adjunct".

The purpose of BLS is to maintain adequate ventilation and circulation until a means can be obtained to reverse the underlying cause of the arrest. It is therefore a "holding operation", although on occasion, particularly when the primary pathology is respiratory failure, it may itself reverse the cause and allow full recovery.

History

The earliest reference to mouth-to-mouth ventilation is considered to be in the Bible, when God created Adam,[10] and when the prophet Elisha revived an apparently dead child.[11] An early medical report of success was reported by Tossach in 1744.[61] After this report, however, there was no further progress with the technique, and attention was turned towards manual methods such as those described by Silvester,[67] Schafer[64] and Holger Nielsen.[33] It is possible that the prudery of the Victorian era prevented acceptance of any method which involved lip contact, but it was not until the 1950s that mouth-to-mouth ventilation was rediscovered and became accepted universally as the method of choice. The inefficiency of the manual methods has led to them being abandoned.[59]

Closed chest cardiac massage was first described in 1878 by Boehm[61] and used successfully in a few cases of cardiac arrest over the next 10 years. After that, however, open chest massage became the standard management for cardiac arrest until 1960, when the classic article on closed chest massage by Kouwenhoven, Jude and Knickerbocker was published.[44] As this coincided with the rebirth of mouth-to-mouth ventilation, 1960 could be considered the year in which modern cardiopulmonary resuscitation was born.

Does BLS work?

Approximately 70% of all cases of cardiac arrest occur out of hospital, often in the victim's home.[27] Early intervention by a bystander—calling for the emergency services and initiating CPR—can materially improve eventual outcome.[18] The sooner that BLS can be instituted the better is the outcome.[21] The concept of the "chain of survival" (see fig. 1) emphasizes that optimum results can be achieved only with the four elements of: early access, early CPR, early defibrillation and early advanced cardiac life support.[19] Most cases of survival from cardiac arrest occur when the victim is in ventricular fibrillation, and the effect of CPR is to prevent this rhythm from degenerating into asystole,[74] the prognosis for which is poor.[77] The provision of a defibrillator at the earliest possible opportunity is of prime importance. The longer the delay before this can be achieved, the more important is the provision of CPR.[12] The opposite is also the case; where the emergency back-up is so well advanced that a defibrillator can be provided on scene within 3–4 min, initial CPR is of little benefit.[71]

For a witnessed, out-of-hospital cardiac arrest when the victim is in ventricular fibrillation, a survival rate to leaving hospital of approximately 30% should be possible.[23] Recent reports show that this can be achieved in Europe.[25]

If cardiac arrest occurs in hospital, the outcome depends on the underlying condition of the patient[41]: approximately 15% may be expected to

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Key words
Complications, cardiac arrest. Heart, resuscitation. Basic life support.

ANTHONY J. HANDLEY, MD, FRCP, Department of Medicine, Colchester General Hospital, Turner Road, Colchester, Essex CO4 5JL.

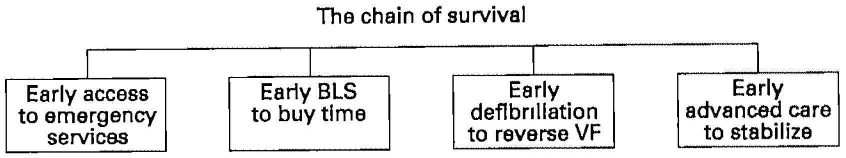
The chain of survival
Early access to emergency services
Early BLS to buy time
Early defibrillation to reverse VF
Early advanced care to stabilize

Figure 1 The concept of "chain of survival". The concept emphasizes that optimum results can be achieved only with the four elements of: early access, early CPR, early defibrillation and early advanced cardiac life support. BLS=Basic life support, VF=ventricular fibrillation.

leave hospital alive.[73] For these patients, CPR may play a much lesser role compared with defibrillation and advanced life support.[41]

BLS guidelines

Since 1975 the American Heart Association has periodically issued standards and guidelines for the performance of resuscitation including BLS.[24,68,69,70] These guidelines have been followed by many organizations throughout the world, but there have also been numerous variations. In 1992 the European Resuscitation Council issued guidelines particularly appropriate to the emergency care facilities available within Europe.[5] The Resuscitation Council (UK) adopted these guidelines which then became the standard for this country.[26]

In 1993 the Basic Life Support Group of the International Liaison Committee on Resuscitation (ILCOR) was formed to review existing BLS guidelines from around the world, and to produce a document, or "advisory statement", that could be used as a resource by organizations wishing to develop their own guidelines. The group consists of representatives from resuscitation councils throughout the world, including the American Heart Association, Australian Resuscitation Council, European Resuscitation Council, Heart and Stroke Foundation of Canada, and Resuscitation Council of Southern Africa. An "advisory statement" on BLS (and on advanced life support and paediatric life support) has now been produced.[37] This advisory statement has been adopted, with minor modifications, by the Resuscitation Council (UK) and is presented below.

Even though the value of early, bystander CPR is universally recognized and public CPR programmes have been in existence for approximately 30 yr, most communities still fail to train a sufficiently high proportion of the public to perform basic life support.[27] Paradoxically, in some high-risk populations, the likelihood of bystander CPR being performed is particularly poor.[8,23]

The special challenge when producing guidelines for BLS is to make them equally applicable for use by members of the general public and by health care professionals.

The BLS group of ILCOR set itself four objectives—the advisory statements had to: (a) embrace modern scientific opinion; (b) be as simple as possible to aid skill retention; (c) be the best advice available whatever the cause or nature of the cardiopulmonary arrest; (d) be acceptable to all countries and organizations

Inevitably, objectives (c) and (d) required compromise decisions. Some variations had to be incorporated to allow for the different causes of collapse, particularly the difference between primary respiratory and primary cardiac arrest. It was also accepted that differences in the level of national and local emergency medical services would dictate the optimum point in the resuscitation attempt when the lone rescuer should leave the victim to go to obtain help.

What should be taught?

What the public is taught must be based on the most up-to-date available scientific evidence. BLS skills have to be taught, learnt and remembered, yet are often only used for the first time months or years later. It is well recognized that skill decay is rapid, even among professionals.[9,15,54] This may be caused partly by poor standards of teaching,[42] but partly also by the highly complex nature of the psychomotor skills involved. Within 4 months of being trained, 50% of first aiders were unable to perform adequate CPR on a manikin[35]; 6 months after a public course in BLS, only approximately 7% of those attending were deemed able to perform safe and effective CPR.[51]

The psychomotor skills required for BLS are particularly susceptible to rapid decay. Almost 50 separate skills are needed to perform the current sequence of CPR, which is partly the reason why learning and retention are difficult.[30] Clearly it would be possible to simplify BLS techniques for the lay person to no more than "pump and blow". In contrast, far more complicated procedures than those currently published could be developed by the addition of more comprehensive assessment of the victim, and different emphasis of management depending on the aetiology of the respiratory or cardiac arrest. It is not known how "simple" training could be made in order to aid skill retention, while still maintaining clinical effectiveness.

There is uncertainty within the literature regarding how "good" CPR has to be in order to save a life.[45] Do victims who receive perfectly performed compressions and rescue breathing (so called "good CPR") fare better than victims who receive less effective CPR? A definitive answer is still awaited, but the clear conclusion from many studies is that the lowest survival rates occur when there is no attempt at CPR.[12] Any CPR is better than no CPR. Therefore, a simple, basic approach that can be taught effectively to the largest number of people should help to increase the pool of individuals willing to attempt BLS.

The following *sequence of actions* is aimed primarily at the single lay rescuer dealing with an adult victim. Health care providers and emergency personnel are likely to possess extended resuscitation skills, and the situations in which they may be called upon to use these skills often require more complicated BLS guidelines. The underlying principles, however, remain the same.

These guidelines are intended for the resuscitation of adults, but the principles can be applied effectively to infants and children. Guidelines specific to infants and children are discussed elsewhere in this issue of the journal. In the following descriptions, the masculine includes the feminine.

Sequence of actions (fig. 2)

1. *Ensure safety of rescuer and victim.*
2. *Check the victim and see if he responds.*
- Gently shake his shoulders and ask loudly: "Are you all right?"

3A. *If he responds by answering or moving.*
- Leave him in the position in which you find him (provided he is not in further danger), check his condition and get help if needed.
- Reassess him regularly

3B. *If he does not respond.*
- Shout for help.
- Open his airway by tilting his head and lifting his chin: if possible with the victim in the position in which you find him, place your hand on his forehead and gently tilt his head back keeping your thumb and index finger free to close his nose if rescue breathing is required; at the same time, with your fingertip(s) under the point of the victim's chin, lift the chin to open the airway; if you have any difficulty, turn the victim onto his back and then open the airway as described. Avoid head tilt if trauma to the neck is suspected.

4. *Keeping the airway open, look, listen and feel for breathing (more than an occasional gasp).*

Look for chest movements; listen at the victim's mouth for breath sounds; feel for air on your cheek.
- Look, listen and feel for *up to 10 s* before deciding that breathing is absent.

5A. *If he is breathing (other than an occasional gasp).*
- Turn him into the recovery position.
- Check for continued breathing.

5B. *If he is not breathing.*
- Send someone for help or, if you are on your own, leave the victim and go for help (see below); return and start rescue breathing as below.
- Turn the victim onto his back if he is not already in this position.
- Remove any visible obstruction from the victim's mouth, including dislodged dentures, but leave well fitting dentures in place.
- Give two *effective* rescue breaths, each of which makes the chest rise and fall: ensure head tilt and chin lift; pinch the soft part of his nose closed with the index finger and thumb of your hand on his forehead; open his mouth a little, but maintain chin lift; take a breath and place your lips around his mouth, making sure that you have a good seal; blow steadily into his mouth for approximately 1.5–2 s watching for his chest to rise; maintaining head tilt and chin lift, take your mouth away from the victim and watch for his chest to fall as air comes out.
- Take another breath and repeat the sequence as above to give two effective rescue breaths in all.
- If you have difficulty achieving an effective breath: re-check the victim's mouth and remove any obstruction; re-check that there is adequate head tilt and chin lift; make up to five attempts in all to achieve two effective breaths; even if unsuccessful, move on to assessment of circulation.

6. *Assess the victim for signs of a circulation.*
- Look for any movement, including swallowing or breathing (more than an occasional gasp).
- Check the carotid pulse.
- Take no more than 10 s to do this.

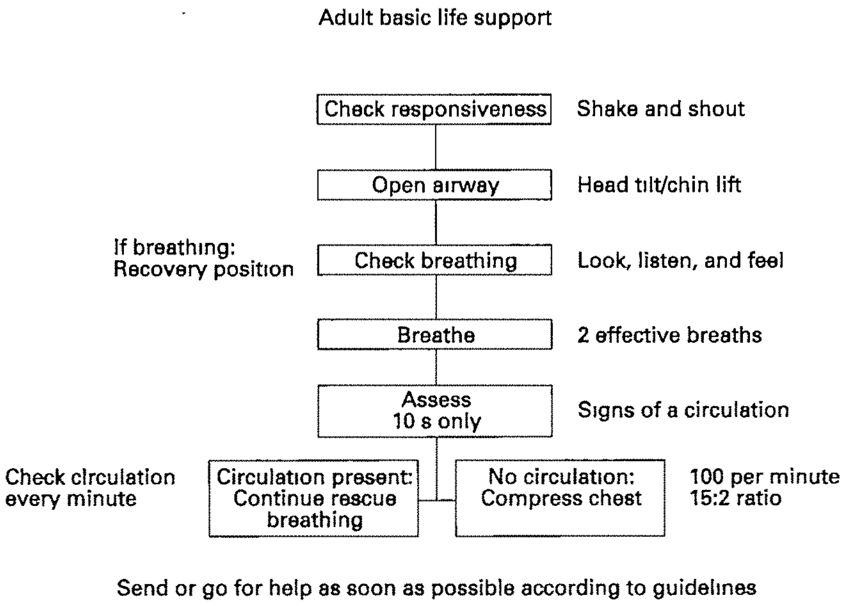
Adult basic life support
Check responsiveness
Shake and shout
Open airway
Head tilt/chin lift
If breathing: Recovery position
Check breathing
Look, listen, and feel
Breathe
2 effective breaths
Assess 10 s only
Signs of a circulation
Check circulation every minute
Circulation present: Continue rescue breathing
No circulation: Compress chest
100 per minute 15:2 ratio
Send or go for help as soon as possible according to guidelines

Figure 2 Algorithm for adult basic life support. The sequence of actions is aimed primarily at the single lay rescuer dealing with an adult victim.

7A. *If you are confident that you can detect signs of a circulation within 10 s.*

- Continue rescue breathing, if necessary, until the victim starts breathing on his own.
- Approximately every minute re-check for signs of a circulation; take no more than 10 s each time.
- If the victim starts to breathe on his own but remains unconscious, turn him into the recovery position. Check his condition and be ready to turn him onto his back and re-start rescue breathing if he stops breathing.

7B. *If there are no signs of a circulation, or you are at all unsure.*

- Start chest compression: locate the lower half of the sternum and place the heel of one hand there, with the other hand on top of the first; interlock the fingers of both hands and lift them to ensure that pressure is not applied over the victim's ribs. Do not apply any pressure over the upper abdomen or bottom tip of the sternum; position yourself vertically above the victim's chest and, with your arms straight, press down on the sternum to depress it between 4–5 cm (1.5–2 in); release the pressure, then repeat at a rate of approximately 100 times a minute (a little less than two compressions a second). Compression and release should take an equal amount of time.
- Combine rescue breathing and compression: after 15 compressions tilt the head, lift the chin and give two effective breaths; return your hands immediately to the correct position on the sternum and give another 15 compressions, continuing compressions and breaths in a ratio of 15:2.

8. *Continue resuscitation until:*

The victim shows signs of life, qualified help arrives or you become exhausted.

Readers will note a number of changes between this sequence of actions and the BLS guidelines adopted by the Resuscitation Council (UK) in 1992.[39] Many of the changes are minor and represent consensus agreement. However, there are a number of topics where an explanation of how the final decisions were reached is of value.

Volume and rate of ventilation

Rescue breathing has been a well accepted technique of airway management in BLS since the early 1960s.[60] The volume of air required for each inflation has been quoted as 800–1200 ml, with each breath taking 1–1.5 s.[24]

Artificial ventilation without airway protection (such as tracheal intubation) carries a high risk of gastric inflation, regurgitation and pulmonary aspiration.[6] The risk of gastric inflation depends on: (a) proximal airway pressure, which is determined by tidal volume and inflation rate; (b) alignment of the head and neck, and degree of patency of the airway; and (c) opening pressure of the lower oesophageal sphincter (approximately 20 cm H_2O).[57]

It has been shown recently that a tidal volume of 400–500 ml is sufficient to provide adequate ventilation in adult BLS because carbon dioxide delivery during cardiac arrest is very low.[7 34] Although this value is lower than that recommended previously, it is consistent with the accepted teaching that tidal volume should be that which causes the chest to rise as in normal spontaneous breathing.

During combined rescue breathing and chest compression, the rate of ventilation is dependent on both the ventilation volume and compression rate. An inflation time of 1.5–2 s diminishes the risk of exceeding the oesophageal opening pressure and results in an inflation/exhalation cycle of approximately 3 s. A chest compression rate of approximately 100 per minute is recommended (see below). It therefore takes 9 s to perform 15 cardiac compressions. Allowing 6 s for the two rescue breaths, single rescuer CPR should result in about 8 breaths and 60 chest compressions per minute.[6]

Circulatory assessment

The single most important sign of cardiac arrest in an unconscious, non-breathing adult has always been the absence of a carotid pulse. Current teaching is that pulselessness should lead to the initiation of chest compression. The time allowed to feel for the pulse differs between resuscitation councils[5 24 43] but none recommends more than 10 s for a normothermic victim, as time is critical when starting CPR.

Should the "carotid pulse check" still be taught as the sole criterion for the initiation of chest compression? Is the carotid pulse check in fact difficult, particularly for lay persons?

Recent studies have strongly suggested that the time needed to diagnose with confidence the presence or absence of a carotid pulse is far greater than the 5–10 s normally recommended, with times in excess of 30 s being needed to achieve a diagnostic accuracy of 95%.[2 28 29 47] Even with prolonged palpation, 45% of carotid pulses may be pronounced absent when in fact present.[20] It should also be borne in mind that most of the studies were undertaken using normotensive volunteers, a situation far different from finding a collapsed, cyanosed victim in the street who is likely to be hypotensive, vasoconstricted or worse.

Many ambulance services offer CPR instruction over the telephone to callers reporting victims who have collapsed. The criteria for advising CPR are normally a combination of unresponsiveness and lack of breathing.[48] It is not usual practice for the dispatcher to ask for a carotid pulse check before advising chest compression, mainly because of the perceived difficulty in describing the technique over the telephone.

As a result of these considerations the BLS group of ILCOR has recommended that the carotid pulse check should be "de-emphasized" and that other criteria should be used to determine the need for chest compression in an unresponsive, apnoeic adult patient. It was decided to use the expression: "Look for signs of a circulation", to include looking for movement and checking the carotid pulse. The rescuer should limit the time taken for this check to no more than 10 s. Therefore, absence of any obvious signs of life, not necessarily absence of the carotid pulse, should be sufficient indication to initiate chest compression.

It should be emphasized that this departure from current teaching is aimed, at least for now, only at the lay rescuer; checking for a pulse remains an important part of advanced life support and the algorithm for use of automatic external defibrillators.

Rate of chest compression

The original term "cardiac massage" and its successor "external cardiac compression" reflect the initial theory as to how chest compressions achieve an artificial circulation—namely, by squeezing the heart. This "heart pump theory"[44] was criticized in the mid-1970s, first because echocardiography demonstrated that the cardiac valves become incompetent during resuscitation[55 76] and, second, because coughing alone was shown to produce a life-sustaining circulation.[17] The alternative "thoracic pump" theory[58] proposes that chest compression, by increasing intrathoracic pressure, propels blood out of the thorax; forward flow occurs because veins at the thoracic inlet collapse while the arteries remain patent.

An extension of the controversy raised by these conflicting theories is the argument as to whether or not the rate of chest compression during resuscitation should be fast or slow. In practice, compression rates of 40–120 per minute have successfully resuscitated patients in cardiac arrest; changes in national and international recommendations reflect mainly changes in consensus opinion. It is important, however, to recognize that even when performed optimally, chest compressions do not achieve more than 30% of the normal cerebral perfusion.[61]

Because a more rapid rate of chest compression is required in infants and children, and because simplification of the guidelines is seen as an important objective, a universal compression rate of 100 per minute (expressed for the lay person as: "a little slower than two a second") seems an admirable compromise.

What is important, however, is that the compression and relaxation phases should each occupy about half the compression: relaxation cycle in order to maximize blood flow.[75] In practice, this is difficult to achieve.[38]

Call first—call fast

The first link in the "chain of survival"[19] is to gain access to the emergency medical services. Advice as to the optimum time during a resuscitation attempt at which to leave the victim to go for help depends on several factors: whether the rescuer is alone; whether the victim has a primary respiratory or primary cardiac arrest; the distance to the nearest point of aid (for example a telephone); and the facilities offered by the emergency services.

The importance of early defibrillation in the treatment of sudden cardiac death is now accepted, and major initiatives are moving forward to deliver a defibrillator and the first shock at the earliest possible moment.[22] The 1992 AHA guidelines[24] emphasized that the rescuer should, if no other help is available, leave an adult victim immediately after establishing unresponsiveness in order to call an ambulance or emergency medical service ("phone first"). The ERC guidelines[5] advise that a shout for assistance should be made as soon as the victim is found to be unconscious, but that the loan rescuer should not leave to go for help until cardiac arrest is diagnosed by means of a pulse check ("phone fast"). Both the AHA and ERC guidelines seek to ensure that a defibrillator reaches the victim at the earliest appropriate opportunity. Both agree that if the victim is a child, the rescuer should provide rescue support (ventilatory or circulatory or both) for about 1 min before leaving the victim and calling the rescue team.[50]

In children the aetiology of cardiopulmonary arrest is different from that of the adult.[40] Respiratory arrest is far more common than cardiac arrest which, if it occurs, is usually secondary to respiratory arrest. The outcome of attempts at resuscitation from cardiac arrest in children is dismal at best, with a high chance of poor neurological status afterwards.[65] Survival after cardiopulmonary arrest in children is dependent mainly on the immediate provision of effective rescue breathing,[31] hence the recommendation of 1 min rescue support before leaving and phoning for help.

Although the current (and proposed) guidelines define a child as up to the age of an adult (presumed 18 yr), there is evidence that the increased frequency of primary respiratory arrest persists until approximately 30 yr of age.[1 49] A difficulty that would be encountered using this age as the cut-off between going for help at once or undertaking initial basic life support, would be finding a way of describing (particularly to the lay person) how to determine the age of the collapsed adult victim. As so often is the case, a "best compromise" wins the day.

In the USA a "call first" policy exists, with full emergency service dispatch taking place if a victim is reported to be unresponsive. The ambulance service in the UK is moving towards the US model of priority-based dispatch, and when an emergency call is received, the caller is now usually asked whether the victim is conscious or unconscious, breathing or not breathing. Unlike the US system, however, a top priority dispatch takes place only if the victim is unconscious and not breathing. As already discussed, the presence or absence of a pulse is not a factor in determining priority further. Because of the different policies of the two countries, the Resuscitation Council (UK) advises that the time for the lone rescuer to leave the victim to go for help should normally be immediately after establishing absence of breathing.

There is a further argument against giving two breaths before a rescuer leaves the victim. It has been shown that in some communities there is a reluctance to perform rescue breathing, or a delay in starting ventilation, on a stranger because of concern over disease transmission, particularly the fear of contracting HIV.[14 53] By advising that a call to the ambulance service should be made as soon as the absence of breathing has been established, help can be found with the minimum of delay.

For of all these reasons, the Resuscitation Council (UK) has endorsed the following advice:

When to get help

It is vital for rescuers to get help as quickly as possible.

- When more than one rescuer is available, one should start resuscitation while another rescuer goes for help.
- A lone rescuer has to decide whether to start resuscitation or to go for help first. In these circumstances, if the likely cause of unconsciousness is trauma (injury), drowning *or* if the victim is an infant or a child, the rescuer should perform resuscitation for *approximately 1 min* before going for help.

If the victim is an *adult*, and the cause of unconsciousness is *NOT* trauma or drowning, the rescuer should assume that the victim has a heart problem and go for help immediately after establishing unresponsiveness and the absence of breathing

Recovery position

The airway of an unconscious victim who is breathing spontaneously is at risk of obstruction by the tongue and from inhalation of mucus and vomit. Placing the victim on the side helps to prevent these problems, and allows fluid to drain easily from the mouth. This lateral, coma, side or recovery position, has been advocated in anaesthesia for more than 100 yr[13] and is still standard practice today. It is surprising, therefore, that its introduction into first aid practice was only within the past 50 yr.[63] Perhaps even more surprising is that in 1992 there was no mention of a recovery position in the AHA guidelines.[24]

Some compromise is needed when positioning the victim; a true lateral posture tends to be unstable, involves excessive lateral flexion of the cervical spine and results in less free drainage from the mouth. A near-prone position, on the other hand, can result in under ventilation because of splinting of the diaphragm and reduction in pulmonary and thoracic compliance.[62]

Potential injury to the victim has also to be considered.[3] There have been several recent reports of interference with upper limb blood flow in association with the recovery position advocated by the European Resuscitation Council.[32 36] This involves the lowermost arm being brought into a ventral position with the uppermost arm crossing it and producing a pressure effect on the blood vessels and, possibly, the nerve supply. Placing the lowermost arm in a dorsal position may not necessarily be the answer, as this involves movement that could, at least theoretically, injury the shoulder joint. However, it is the compromise chosen by the Resuscitation Council (UK) for its 1997 guidelines.

There is inadequate published evidence for definite conclusions but the recognition of the potential for harm and benefit from placing the victim on the side must be remembered.

Many different versions of the recovery position exist, each with its own advocates. The BLS group of ILCOR concluded that it was unable to recommend one specific position, but instead agreed on six principles that should be followed when managing the unconscious, spontaneously breathing victim:

1. The victim should be in as near a true lateral position as possible with the head dependent to allow free drainage of fluid.
2. The position should be stable.
3. Any pressure on the chest that impairs breathing should be avoided.
4. It should be possible to turn the victim onto the side and return to the back easily and safely, having particular regard to the possibility of cervical spine injury.
5. Good observation of, and access to, the airway should be possible.
6. The position itself should not give rise to any injury to the victim.

The future

If one adheres strictly to the definition of basic life support as the maintenance of an airway and support of breathing and circulation without the use of equipment, there is limited scope for improving the current techniques.

Based on the "thoracic pump" theory of chest compression, the greater the intrathoracic pressure produced, the better should be the forward flow of blood. Experimentally this has been achieved by simultaneous compression and ventilation, but intubation with a cuffed tracheal tube is needed to protect the airway from refluxing gastric contents, and to avoid gastric insufflation.[16] Increasing intra-abdominal pressure by the use of an abdominal "vest" also results in an improvement in blood flow during cardiac arrest, but again requires the use of equipment.[66]

Within the strict definition of basic life support, improvement in aortic arterial pressure has been achieved during cardiac arrest without any extraneous equipment by simultaneous chest and abdominal compression,[4] and by increasing the rate of chest compression to 120 per minute.[72] There has also been a tentative suggestion that a return to open chest CPR might be of benefit in some cases.[56]

It is important, however, to bear in mind that there is no published evidence that any of these techniques produce a significant improvement in the outcome of cardiac arrest in the human victim.

The use of a device (Ambu CardioPump) to produce "active compression–decompression" CPR is currently creating a lot of interest, and a flurry of articles in the resuscitation literature. The principle of this device is based on a case described in 1990 of a human resuscitated with the help of a "plumber's helper", better known in the UK as a plunger used for unblocking sink and WC outflows.[46] A rubber suction cup is used alternately to compress then re-expand the chest, thus improving venous return. The reports are encouraging, but proof of increased survival after cardiac arrest is still awaited.[52] If this is forthcoming, the device may represent an important advance in basic life support, albeit with the use of an adjunct.

For the time being, the way to improve survival, particularly in out-of-hospital cardiac arrest, lies with increased public education in the basic techniques of rescue breathing and chest compression, linked closely to greater awareness of the need to call early for the emergency services and the provision of first responder defibrillation.

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Management of the airway and ventilation during resuscitation

D. A. GABBOTT AND P. J. F. BASKETT

The management of the airway and ventilation is a vital component in the resuscitation of patients with respiratory and cardiac arrest.

In recent years considerable emphasis has been placed on the cardiac and vascular elements of resuscitation as the value of early defibrillation has become appreciated as the principal element in producing a return of spontaneous circulation in those with cardiac arrest.[31, 39] Nevertheless, the role of maintaining oxygenation during the resuscitative process is no less important in order to ensure protection of the vital organs from hypoxic damage. In June 1996 the Airway and Ventilation Management Working Group of the European Resuscitation Council published their guidelines for the basic and advanced management of the airway and ventilation during resuscitation.[34, 35] Since then several national resuscitation councils in continental Europe, the UK, Australasia and Southern Africa have adopted these guidelines in principle.

The airway in resuscitation

Airway obstruction may be a prime cause of cardiorespiratory arrest or may occur as a consequence of unconsciousness. Common causes are listed in figure 1. Untreated, the wholly obstructed airway will, within a very short period (generally accepted as 2–5 min except in unusual circumstances, e.g. hypothermia or intoxication with sedative or opioid drugs) cause neurological or other vital systemic damage which may be irreversible or fatal.

BASIC ASSESSMENT

Assessment of the airway is based on a check for unresponsiveness, examining chest movements and feeling for air flow from the mouth and nose. The assessment should be made in the position in which the patient is found, especially if trauma is suspected (see below). If breathing is absent the patient should be turned to the supine position (using manual in-line stabilization of the head and neck if there is a potential cervical spine injury). The head and neck

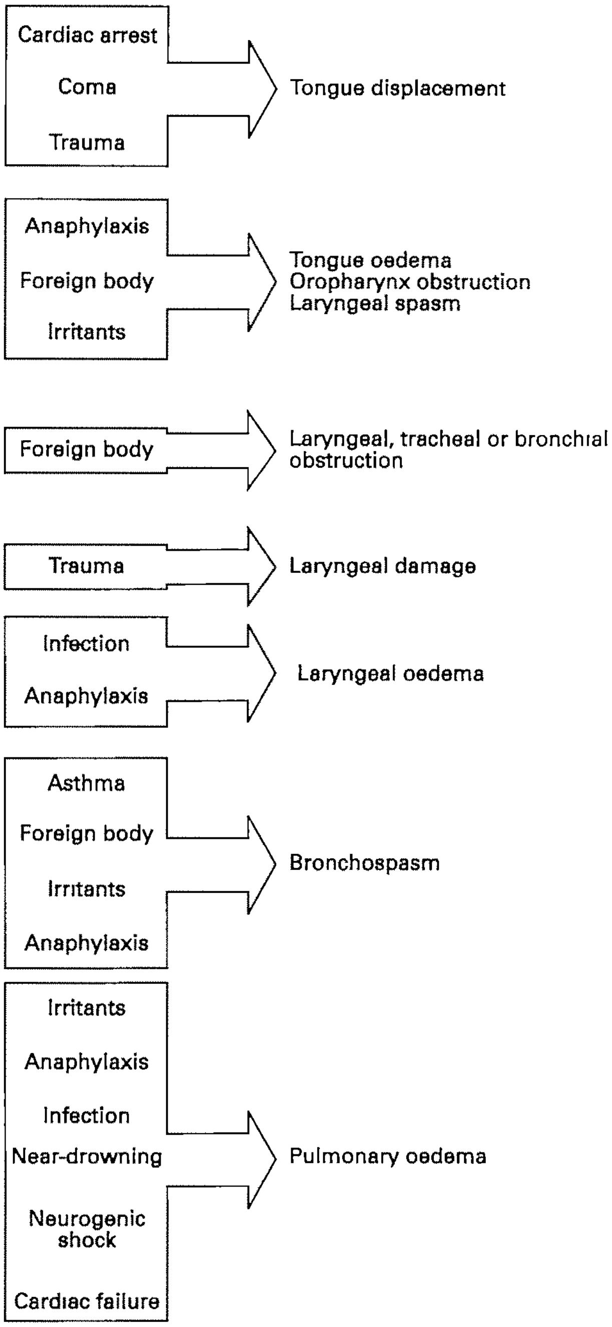

Figure 1 Common causes of airway obstruction.

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Key words
Airway. Heart resuscitation. Complications, cardiac arrest. Ventilation, resuscitation.

D. A. GABBOTT, MA, FRCA, Gloucestershire Royal Hospital, Great Western Road, Gloucester GL1 3NN. P. J. F. BASKETT, BA, FRCA, MRCP, Frenchay Hospital, Bristol BS16 1LE.

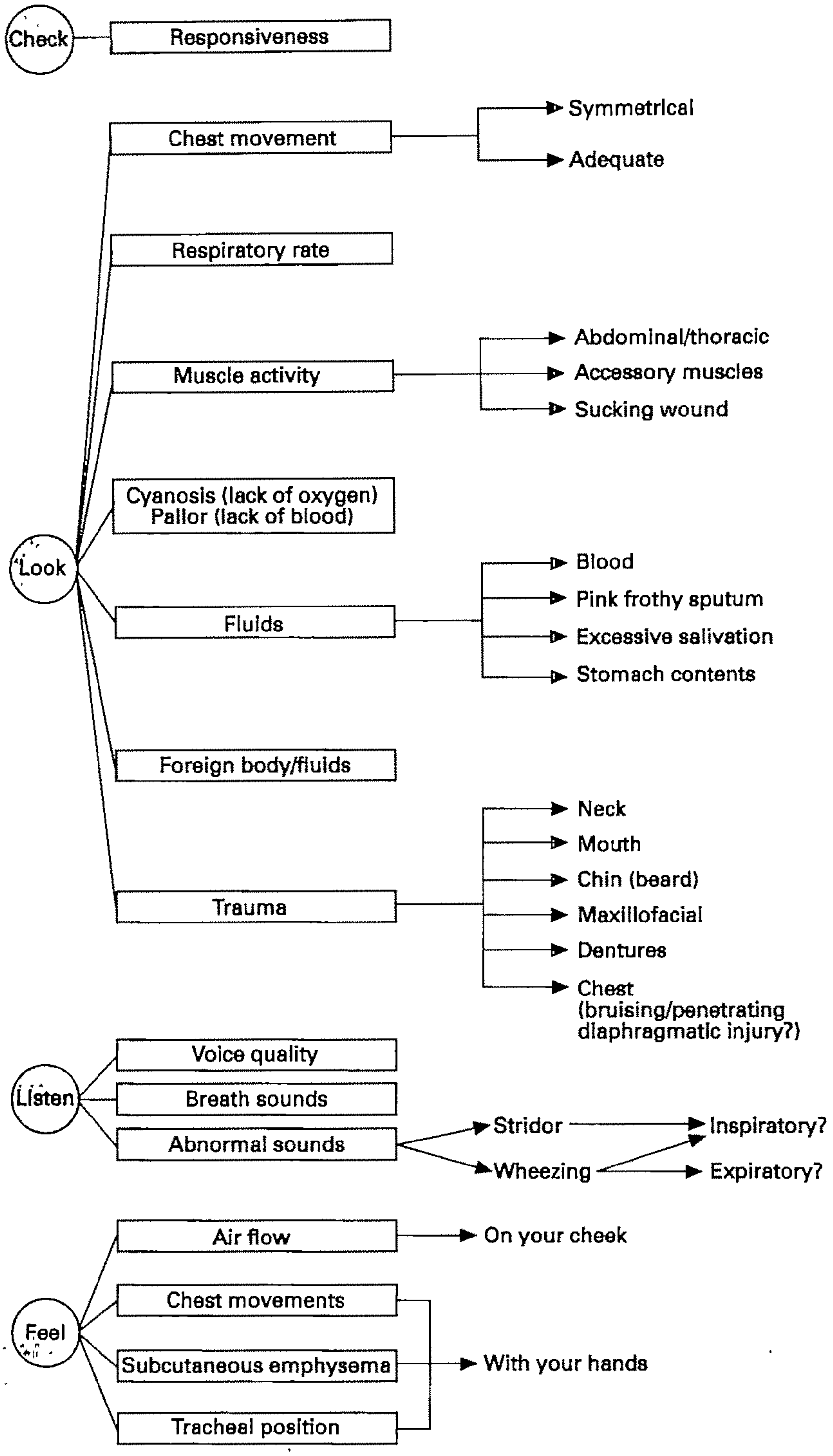

Figure 2 Suggested plan for assessment of the airway and ventilation.

should be aligned in the clear airway position using head and chin lift tilt (omitted if there is a possibility of cervical spine injury), and jaw thrust. Ideally, the head should be placed on a small pillow to achieve the "sniffing the morning air position". When the head and neck are aligned the assessment should be complemented by seeking other signs, such as cyanosis, pallor, excessive salivation, gastric contents or foreign body in the mouth or pharynx, and evidence of head, maxillofacial, neck or chest trauma. Abnormal phonation or breath sounds and wheeze or stridor indicate a particularly obstructed airway. Stridor occurring during inspiration generally indicates obstruction above the larynx, wheeze occurring during expiration usually indicates obstruction below the larynx. A suggested plan for assessment of the airway and breathing is shown in figure 2.

Management of the upper airway obstructed by foreign material (choking)

CAUSES AND SIGNS

In adults the commonest causes are aspiration of

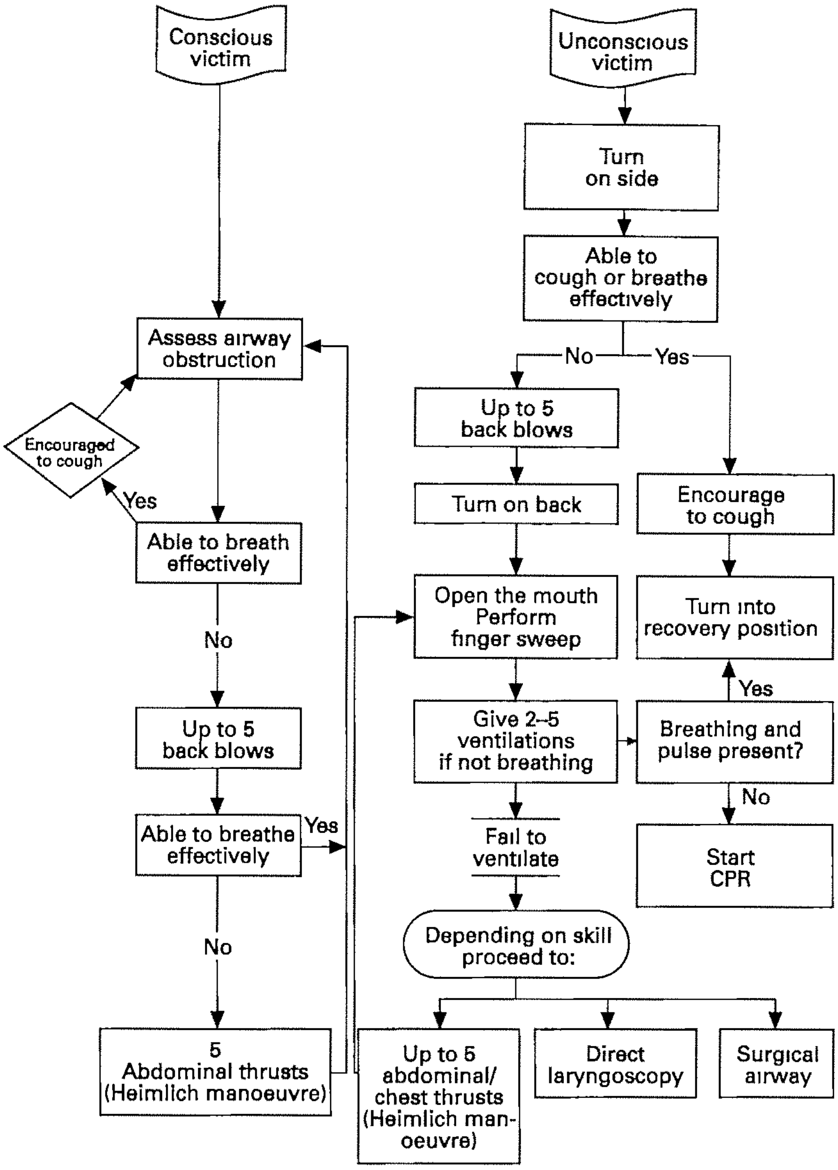
Conscious victim
Assess airway obstruction
Encouraged to cough
Yes
Able to breath effectively
No
Up to 5 back blows
Able to breathe effectively
Yes
No
5 Abdominal thrusts (Heimlich manoeuvre)
Unconscious victim
Turn on side
Able to cough or breathe effectively
No
Yes
Up to 5 back blows
Turn on back
Open the mouth Perform finger sweep
Give 2–5 ventilations if not breathing
Fail to ventilate
Depending on skill proceed to:
Up to 5 abdominal/ chest thrusts (Heimlich manoeuvre)
Direct laryngoscopy
Surgical airway
Encourage to cough
Turn into recovery position
Yes
Breathing and pulse present?
No
Start CPR

Figure 3 Algorithm for the management of upper airway obstruction caused by foreign materical (choking).

gastric contents or blood associated with loss of the protective laryngeal reflexes and choking on large portions of poorly chewed food. In children and the mentally challenged, a large number of other ingested articles may be added to these causes, for example peanuts, marbles, pen tops, beads, etc. Choking is heralded by respiratory distress, stridor, wheezing and coughing. As the obstruction becomes more complete, airflow is reduced, the patient is unable to speak or breathe and cyanosis occurs. Unconsciousness supervenes and death occurs if the obstruction is not relieved immediately. The patient may clutch or point to his or her neck—a universal distress signal for imminent choking.

MANAGEMENT

While there appears to be adequate air movement the patient should be encouraged to cough and be observed closely. Oxygen, if available, should be administered. If air movement is poor or absent and the patient becomes cyanosed, immediate positive action is required. The obstruction may be cleared by head and neck alignment, back blows, abdominal or chest thrusts, lateral positioning or finger sweeps, or by using a laryngoscope with suction, Magill forceps or a Kelly clamp to remove the obstruction under direct vision. As a last resort upper airway obstruction may be bypassed by a surgical airway using cricothyroidotomy or needle jet ventilation provided the appropriate skills and equipment are available.

Back blows

A series of five back blows are applied during expiration with the patient standing, sitting or in the lateral position. Preferably the head should be positioned below the chest to achieve the best gravitational drainage advantage. Children should be placed prone with a head down tilt on the rescuer's thigh or arm. If this fails to clear the obstruction, abdominal thrusts should be used.

Abdominal thrusts (Heimlich manoeuvre)

Abdominal thrusts may be applied with the patient standing, sitting or lying down in the supine position. The supine position is used in unconscious patients and in the very obese or when the rescuer finds it impossible to encircle the abdomen of the victim. Abdominal thrusts may result in damage to the abdominal viscera or gastric regurgitation. The technique is not recommended in infants and small children[33] or in advanced pregnancy.

The guidelines of the American Heart Association[32] do not recommend the application of back blows in adults (although they do in infants and small children[73]) and prefer early application of abdominal thrusts. European, Australasian and Southern African guidelines advocate the application of back blows before abdominal thrusts.

Chest thrusts

Chest thrusts are preferred in children and when abdominal thrusts are contraindicated or ineffective. Rhythmic thrusts are applied with both hands to the anterior aspect of the chest in the same position as used for external chest compressions.

Finger sweeps

Finger sweeps should be used only in the unconscious victim who does not have good reflexes or the ability to bite the rescuer's finger. The patient should be placed in the lateral position. Blind sweeps are not generally recommended in infants and small children because of the risk of deeper impaction of the foreign body at the laryngeal level but sweeps using the little finger to extricate an obvious object under direct vision are acceptable. An algorithm for the management of choking is shown in figure 3.

The recovery position

The recovery position is used in unconscious patients with adequate spontaneous breathing to maintain a patent airway and reduce the possibility of aspiration of gastric contents or foreign material in the mouth or pharynx. Several different recovery positions have been advocated (dependent arm behind or in front of the trunk, uppermost arm extended or flexed to place the hand under the cheek, dependent leg extended or flexed, uppermost leg extended or flexed). It has proved impossible to obtain universal international agreement as to the best position but there is consensus as to the principles involved. These principles include:

- The patient should be in as near a true lateral position as possible with the mouth dependent to allow free drainage of fluid.
- The position should be stable.
- Any pressure on the chest that impairs breathing should be avoided.
- Care should be taken to avoid compromise of the circulation in either arm or peripheral nerve compression in the arms and legs.
- It should be easy to turn the victim into the lateral position and return to the supine position, having particular regard to the possibility of injury to the cervical spine.
- Good observation and access to the airway should be possible.

MANAGEMENT OF THE AIRWAY IN PATIENTS WITH SUSPECTED SPINAL INJURY

Great caution must be taken in aligning the head and neck in any trauma victim requiring resuscitation. In these circumstances the cervical spine must be maintained in a neutral mid-line position unless it is physically difficult to do so or resistance is encountered during any attempt at realignment. Manual in-line stabilization is the technique of choice in any trauma patient, with the head grasped firmly at the mastoid processes and the occiput.[52 58] Traction should be avoided as it may distract the cervical spine and cause more neurological damage.[77] Jaw thrust is the only basic airway opening manoeuvre appropriate for any patient with suspected cervical spine injury. Suction and use of forceps under direct vision using a laryngoscope with the head and neck maintained in the neutral position are the best methods of removing foreign material from the mouth and pharynx but back blows and abdominal or chest thrusts are acceptable only in extreme conditions. The risk of hypoxic damage from airway obstruction in an unconscious breathing victim is likely to outweigh the risk of aggravating cervical spine injury in the vast majority of cases and such patients should be placed in the lateral position using a log rolling technique with a minimum of four attendants. The rescuer controlling the head and neck with manual in-line stabilization should be in command of the rotation procedure. When turned, the lower limb should not be flexed unless a thoracolumbar injury is not suspected. Movement of the arms is not recommended.

Basic management of ventilation

In basic resuscitation the method of choice is expired air ventilation using the mouth-to-mouth, mouth-to-nose, mouth-to-mouth-and-nose (neonates) or the mouth-to-mask method. The mouth-to-mask method has aesthetic advantages and may reduce the possibility of cross infection between patient and rescuer. Some models of mask permit the addition of oxygen if available. The hitherto recommended sequence of ventilations in relation to external chest compressions in patients with cardiac arrest has been 1:5 (using two rescuers) and 2:15 (using a single rescuer).[32] Recently, the European Resuscitation Council has recommended that only the single rescuer method (2:15 sequence) should be taught to lay people using the justification that the second person's priority should be to seek and provide help (especially a defibrillator) and that two lay people may find co-ordination of chest compressions and ventilations difficult unless they have practised together regularly. This teaching is likely to be followed on a global scale by authorities in Australasia, Southern Africa, the United States, Canada, Latin America and the Pacific Rim. While there is consensus regarding the technique of application of expired air ventilation there is debate as to the sequence in relation to chest compressions, inflation flow rate and volume of ventilation.

SEQUENCE OF VENTILATIONS AND CHEST COMPRESSIONS

Early guidelines from the American Heart Association (AHA)[68 69] proposed that four ventilations should be given at the beginning of resuscitation using a "step-on-step" technique of applying each subsequent inflation before exhalation was complete, thus introducing a form of positive end-expiratory pressure (PEEP). The rationale behind this practice was the postulation that alveolar collapse occurred with cardiorespiratory arrest and that application of PEEP would improve the situation. The "step-on-step" technique for the first four breaths was rescinded in the guidelines of 1986[70] in the face of evidence that this method generated high proximal airway pressures[40] and that the lower oesophageal sphincter opening pressures were likely to be reduced.[54 81]

Both of these factors were likely to increase the risk of gastric regurgitation and subsequent pulmonary aspiration. The 1986 AHA standards and guidelines reverted to initial application of two normally spaced breaths followed by a one-rescuer sequence (15 compressions/two ventilations) or a two-rescuer sequence (five compressions/one ventilation).

Clearly the 15:2 or 5:1 sequences which were proposed in the late 1950s were based on a concept of normal cardiorespiratory physiology. However, this state of affairs is unlikely to apply in cardiorespiratory arrest when delivery of carbon dioxide to the lungs is likely to be low, so reducing the emphasis on ventilation frequency and volume. What is paramount, however, in cardiac arrest is oxygenation and there is a need for research to establish the best compromise to provide satisfactory oxygenation and carbon dioxide removal under these conditions.

For the future it may be that the frequency of ventilation can be reduced to a sequence of 1 in 10 or even 1 in 20 interposed with external chest compressions while oxygen is insufflated into the lungs. However, in the absence of new positive scientific evidence the principle of adherence to the present recommendations applies.

VENTILATION FLOW RATES AND VOLUMES

Ventilation through an unprotected airway whether using the expired air technique or a self-inflating bag–valve–mask carries a very high risk of gastric inflation and subsequent pulmonary aspiration. Evidence of aspiration has been found in approximately 28% of failed resuscitations examined by the coroner.[45] Weiler, Heinrichs and Dick[81] reported evidence of gastric inflation in two of 31 anaesthetized patients with an unprotected airway ventilated by experts and recommended that inflation pressures should be limited to 20 cm H_2O. The following factors are relevant in considering the possibility of gastric inflation during resuscitation.

- Alignment of the head and neck.
- Lower oesophageal sphincter opening pressures.
- Proximal airway pressure during inflation.

Optimal alignment of the head and neck has been discussed above. The lower oesophageal sphincter opening pressure has been estimated to be in the region of 20 cm H_2O in live patients.[81] In swine subjected to experimental cardiac arrest the oesophageal sphincter opening pressure decreased from 26 to 4 mm Hg.[54] Although there are no comparable data for humans it is likely that a similar decrease occurs as suggested by the high incidence of regurgitation reported during cardiac arrest.[45]

The proximal airway inflation pressure during intermittent positive pressure ventilation is related to the inflation flow rate and tidal volume.

The recommendations of the AHA stipulate that either a tidal volume sufficient to make the chest rise normally, or 800–1200 ml, should be applied over 1–2 s at a rate of approximately 10 bpm.[32] Clearly these numerical volumes aim to achieve hyperventilation.

Training manikins equipped with auditory and visual signals hitherto have been set to conform to tidal volumes of 800–1200 ml. Analysis of these numerical recommendations, however, reveals several difficulties. To maintain inflation pressures at reasonable values (approximately 20 cm H_2O) a tidal volume of, say, 1000 ml requires at least 2.5 s for inflation and another 1 s for exhalation using a single rescuer. Longer times are needed for patients with reduced compliance. Thus two ventilations last at least 7 s, 15 external chest compressions applied at a rate of 80 per minute last 12 s, and therefore the total time for each sequence is (7+12) 19 s. Just over three sequences are completed in 1 minute (i.e. six breaths and 45–50 chest compressions) and while six breaths per minute may be adequate during cardiac arrest, it is unlikely that 45 chest compressions provide a viable circulation. Similar calculations can be performed for a 1:5 sequence with similar results. In considering the alternative component of the recommendations, clinical observation of the chest, it is important to determine the tidal volume associated with a "normal" breath. Baskett, Nolan and Parr showed in anaesthetized patients that adequate chest movement perceived by nurse and medical observers was produced by tidal volumes of 400–500 ml.[11] Calculating the number of chest compressions and ventilations using a tidal volume of, say, 500 ml with the same inflation rate, each sequence would take 3.5 s (two breaths) plus 12 s (15 compressions) = 15.5 s, resulting in just under four sequences per minute, totalling eight breaths and 60 chest compressions.

In clinical resuscitation practice the tidal volume applied is gauged by the rise and fall of the chest and is likely to be approximately 400–500 ml rather than the 800–1200 ml required in manikin practice. It is likely that many victims have survived using tidal volumes of 400–500 ml during resuscitation and certainly the minute volumes generated are more than adequate to clear carbon dioxide during anaesthesia with a normal cardiac output.

For this reason the European, Australasia and Southern African Resuscitation Councils have recommended a tidal volume of 400–500 ml (5–6 ml kg^{-1}) during resuscitation and that training manikins with visual or auditory signals, or both, should

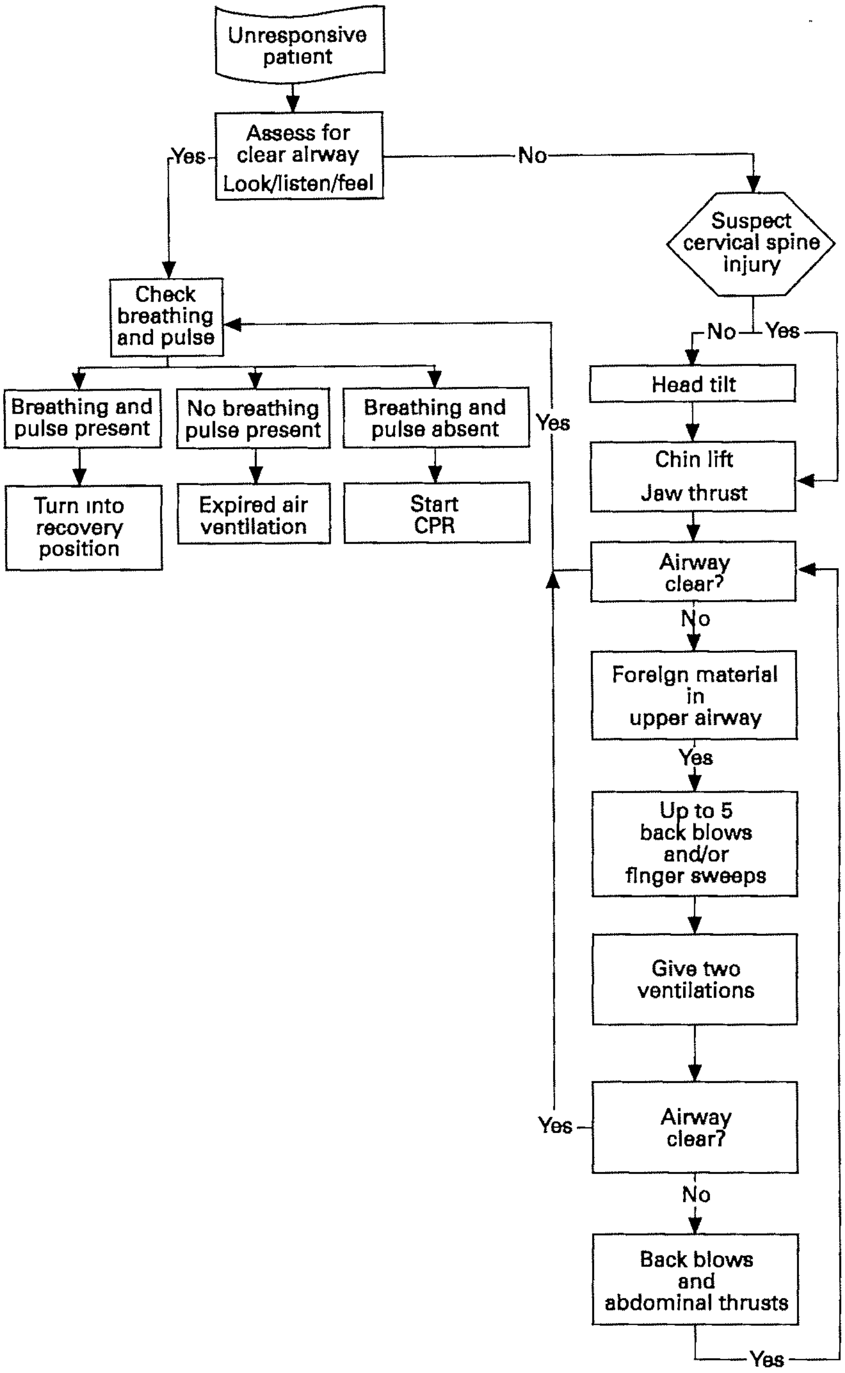
Unresponsive patient
Assess for clear airway Look/listen/feel
Yes
No
Suspect cervical spine injury
No
Yes
Check breathing and pulse
Breathing and pulse present
No breathing pulse present
Breathing and pulse absent
Turn into recovery position
Expired air ventilation
Start CPR
Yes
Head tilt
Chin lift
Jaw thrust
Airway clear?
No
Foreign material in upper airway
Yes
Up to 5 back blows and/or finger sweeps
Give two ventilations
Yes
Airway clear?
No
Back blows and abdominal thrusts
Yes

Figure 4 Flow chart for basic management of the airway and ventilation.

indicate satisfactory inflation at a tidal volume of 400–600 ml.[35]

Many questions remain in this field and can be answered only by research studies which are not easy in patients undergoing resuscitation. Perhaps even smaller tidal volumes would suffice to eliminate carbon dioxide? Would higher compression rates (100–120 per minute) produce better perfusion of vital organs and improved survival rates? Would simple insufflation of oxygen through a patent airway such as a laryngeal mask or tracheal tube provide adequate oxygenation? Given sufficient inspired oxygen concentrations, do standard chest compressions provide adequate pulmonary ventilation to remove the carbon dioxide that is being delivered to the lungs under these circumstances? Or would active compression and decompression of the chest (ACD CPR) using a device such as the Cardiopump (Ambu) be more effective? Does Vest CPR (Cardiologic Systems) provide adequate pulmonary ventilation? These and other questions require an answer before more definitive recommendations can be made in such a fundamental matter as the optimal method of producing satisfactory oxygenation and removal of carbon dioxide during resuscitation. A flow chart for basic management of the airway and ventilation[35] is shown in figure 4.

Advanced management of the airway and ventilation during resuscitation

Advanced airway management is required if basic techniques are proving inadequate or more experienced personnel and equipment are available. Any technique can be described as advanced if it involves the use of adjuncts, and the European Resuscitation Council (ERC) has recently published guidelines on the subject.[34] The use of advanced airway techniques ultimately must be a personal choice depending on the training and experience of the individual concerned.

The ERC algorithm for advanced airway management (fig. 5) begins with the apnoeic patient or an unprotected airway. Clearly basic life support measures may be in progress, for example mouth-to-mouth ventilation or, if the hospitalized patient has developed an immediate need for airway management, advanced techniques may be applied in the first instance.

ADVANCED AIRWAY ADJUNCTS AND TECHNIQUES

Oral and nasopharyngeal airways

These are the simplest of the advanced airway adjuncts. They are easy to insert and help provide a

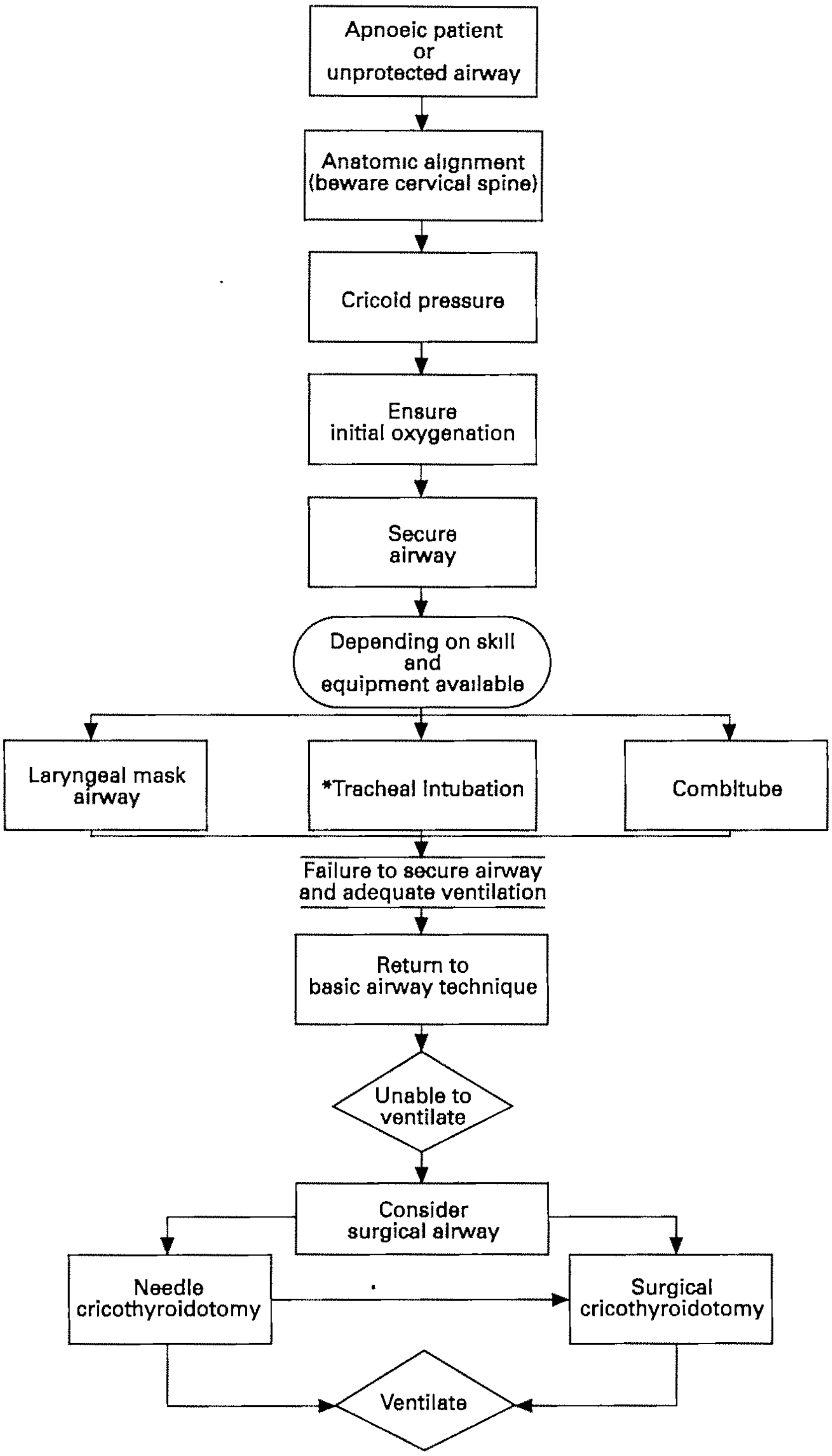
Apnoeic patient or unprotected airway
Anatomic alignment (beware cervical spine)
Cricoid pressure
Ensure initial oxygenation
Secure airway
Depending on skill and equipment available
Laryngeal mask airway
*Tracheal intubation
Combitube
Failure to secure airway and adequate ventilation
Return to basic airway technique
Unable to ventilate
Consider surgical airway
Needle cricothyroidotomy
Surgical cricothyroidotomy
Ventilate

Figure 5 Flow chart for advanced management of the airway and ventilation. *Tracheal intubation is best; the laryngeal mask airway or Combitube are initial alternatives.

patent airway by limiting obstruction by the tongue. They need to be appropriately sized, positioned correctly and used in the relevant circumstances. Oral and nasal airways that are too short are ineffective and those that are too long may provoke laryngeal spasm. Oral airways are poorly tolerated in semi-conscious patients with active gag reflexes and may be difficult to insert in patients with clenched jaws. The nasal airway is often better tolerated in these circumstances. The oral airway can be inserted using the familiar rotational method or with a tongue depressor, which is the favoured method when dealing with children. The nasal route must be used (if at all) with extreme caution in victims of trauma, particularly if a base of skull fracture is suspected. Placement of nasal airways into the cranial vault has been described,[24] furthermore the nasal route is far more likely to cause haemorrhage than the oral route. A recent modification of the oral airway includes a pharyngeal cuff. The COPA airway (Mallinkrodt Ltd) has a standard 22-mm connector and may allow ventilation via a self-inflating bag or anaesthesia system. None of these devices offers any protection from regurgitation of gastric contents.

Cricoid pressure

It is now clear that regurgitation and aspiration must be considered as major hazards during resuscitation if the airway is unprotected. Cricoid pressure represents a protective measure during basic airway management until advanced methods can be applied. The technique is easily taught but requires re-evaluation as many who have been trained in applying it provide widely differing forces to the cricoid cartilage.[44] Recent work suggests that the original value of 44 Newtons required to prevent regurgitation is excessive and a value of approximately 30 Newtons is appropriate.[78] The presence of an oro- or nasogastric tube has been shown in cadaver studies to increase the efficiency of protection provided by cricoid pressure and it should therefore be left *in situ*.[63 78]

The use of cricoid pressure is not without potential problems. If attempts are made to ventilate a patient's lungs manually using a face mask, after applying pressure to the cricoid cartilage, there may be significant reduction in expired tidal volume and an increase in peak inspiratory airway pressure. Furthermore, complete airway obstruction may occur in up to 10% of cases.[2] This may be because of direct airway compression if cricoid pressure is excessive or applied incorrectly. Furthermore, if pressure is applied in a caudal direction (which occurs if the patient's head is flexed on a pillow) this may cause closure of the laryngeal inlet via a rotational effect on the arytenoid cartilages[12] (R. Vanner, personal communication). Cricoid pressure may also cause relaxation of the lower oesophageal sphincter making regurgitation more likely if pressure is applied poorly or released transiently.[75]

Pressure can be applied with one hand or bimanually with a hand supporting the posterior cervical spine. Recent work suggests that the single-handed technique provides just as good a view at laryngoscopy as using two hands.[15] However, supporting the cervical spine with a hand placed beneath the neck is clearly of potential benefit in any victim of trauma with a suspected broken neck. In another recent study, single-handed cricoid pressure caused significant movement of the neutrally positioned cervical spine[26] confirming that in trauma patients, at least, some posterior support of the cervical spine is indicated. Finally, if tracheal intubation is difficult or impossible, the use of other airway adjuncts (e.g. laryngeal mask airway) in the presence of cricoid pressure may be impaired.[4–8 27]

Tracheal intubation

The gold standard for advanced management of the airway during resuscitation is tracheal intubation. This provides a clear and secure airway allowing ventilation, oxygenation and suction. The skill of intubation is not easily taught, requires constant practice and the technique is not without complications if performed poorly or attempts are prolonged. There are a vast array of aids to intubation to help with the difficult airway, including laryngoscopes, bougies, stylets and light wands. Of the currently available accessories, the gum elastic bougie and McCoy laryngoscope appear to be two of the more useful, particularly in cases of difficult intubation of the trauma victim.

The gum elastic bougie has been shown to reduce significantly the failure rate of oral tracheal intubation in patients where manual in-line stabilization and cricoid pressure were applied[58] despite a slightly longer intubation time. The McCoy laryngoscope was introduced in 1993 and is available in sizes 3 and 4 for adults and more recently in sizes 1 and 2 for children. The laryngoscope causes elevation of the epiglottis from a fulcrum deep within the hypopharynx and requires less force than the Macintosh blade to expose the laryngeal structures.[49] The McCoy laryngoscope has also been shown to reduce the stress response to laryngoscopy compared with the Macintosh blade.[48] Studies have demonstrated that the laryngoscope improves the view at laryngoscopy compared with the conventional Macintosh blade and more importantly, the number of difficult views (grades 3 and 4) is reduced significantly.[16 25 43 76]

A variety of other intubation aids are available and include other laryngoscopes (e.g. Bullard, Upsherscope, Wuscope) and lighted stylets. An assortment of tracheal tubes are available with flexible tips (e.g. "Endotrol" tube), and a new stylet, the Rusch intubating stylet, allows the curve of a standard tracheal tube to be manipulated. The techniques of digital and blind nasal intubation have their advocates but both require considerable skill and constant practice. Nasal intubation is probably not appropriate for the trauma victim and furthermore, a survey of ATLS trained personnel revealed a poor success rate for intubation via this route.[50] It is now clear that in experienced hands, oral intubation of the trachea is the preferred method, particularly for the trauma patient.[18 64 66] The view at laryngoscopy is also significantly improved if the cervical collar is removed[36] and if there are enough personnel available this should be done while the neck is stabilized manually.

Confirmation of successful placement of the tracheal tube in resuscitation is of paramount importance and a variety of aids are available. The gold standard is undoubtedly capnography but misleading readings may occur because of reduced carbon dioxide delivery to the lungs in the arrested circulation. Furthermore, the apparatus is often not immediately accessible in resuscitation situations and more simple devices are appropriate. The oesophageal detector[80] is such a device. It has been modified to include the use of an evacuator bulb[59] and is highly sensitive at picking up oesophageal placement of a tracheal tube. A variety of colorimetric carbon dioxide detectors are also available, but these are not always accurate and may fail if there is not enough expired carbon dioxide. They may occasionally register a false positive result as a consequence of carbon dioxide in the stomach, either from poor basic life support techniques associated with gastric inflation or, more rarely, the presence of carbonated drinks in the gastric contents.

A more recent adjunct used for confirmation of successful tracheal intubation is the Scotti airway detector.[56] The device sends sound waves down the tracheal tube and the reflected wave is detected. If the tube is in the trachea, which is hollow, then the reflected wave is different to that detected if the tube is in the oesophagus, which is collapsed. The concept, while simple, is not without problems. The device needs calibrating and a recent study has demonstrated that it is not very specific.[47]

Finally, while the role of flexible fibreoptic laryngoscopy is limited in resuscitation situations, there are now hand-held, battery-operated fibreoptic devices (e.g. Rapiscope; Cook Critical Care Ltd) which, because they are readily portable, may find a role in confirmation of tracheal tube placement. The device has also been used to confirm correct placement of a needle or catheter passed through the cricothyroid membrane during formation of a surgical airway.[65]

Laryngeal mask airway (LMA)

This airway device (fig. 6) has revolutionized anaesthetic practice since its introduction in 1988. More than 1000 scientific studies have testified to its satisfactory and versatile application in a variety of difficult circumstances. The device provides a clear airway without the need for laryngoscopy and it can be inserted from in front of the patient if necessary, which may be useful for victims of entrapment. Ventilation is more efficient and easier than with a bag and face mask[1 53] and it can also be inserted with the neck maintained in a neutral position[13 60] for patients in whom cervical spine trauma is suspected. The technique of insertion is easily taught to nurses, paramedics and doctors[1 19 30 53 61] and the device has been used successfully by all of these groups in the management of cardiac arrest both in and outside hospital.[29 42 74] Training on manikins has been shown recently to be just as effective as training on patients when learning the insertion technique[62] and the recently introduced Portex introducer may encourage an even greater success rate for LMA insertion by non-anaesthetic personnel.[21]

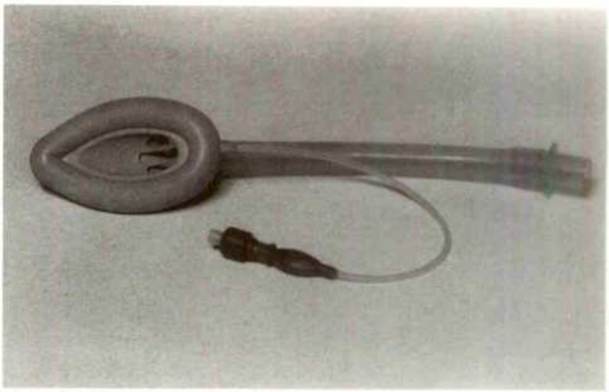

Figure 6 The laryngeal mask airway.

The LMA allows positive pressure ventilation provided it is applied carefully and airway pressures do not exceed 20–25 cm H_2O. In patients with poorly compliant lungs, for example those with pulmonary oedema, aspiration or obstructive airways disease, the lungs may not be ventilated adequately using the device. Inadequate protection of the airway is often quoted as a limitation of the LMA. However, evidence that pulmonary aspiration occurs in clinical practice is scant. In a multicentre study using the LMA at cardiac arrests the reported incidence of aspiration was only 1.5%.[74] Furthermore, the LMA protects the airway against aspiration from sources *above* the larynx.[17 41] This may have profound implications for some types of patients requiring resuscitation. In a recent study of trauma victims,[51] of those who aspirated, the vast majority aspirated blood. In nearly all cases this blood originated from sources above the larynx.

Another potential problem with the LMA is its ability to function adequately in the presence of cricoid pressure. There are several studies[4–8 27] that have suggested that cricoid pressure impedes placement of the device. Furthermore, if cricoid pressure is released and then re-applied after insertion of the LMA, its function may still be impaired.[6] A recent radiographic study[5] showed that cricoid pressure caused upward displacement of the LMA which may allow its aperture to sit against the base of the tongue, thus impairing ventilation.

Despite this, the LMA remains an extremely useful device for resuscitation. Its ease of insertion and effectiveness suggest it should be used as a first-line airway adjunct for those who do not posses the skill to intubate the trachea, such as nurses and many doctors. If oral intubation is proving difficult the device may provide a route for intubation by allowing blind passage of a tracheal tube or gum elastic bougie down the lumen and into then trachea. The success rate for this procedure is variable however, with one study quoting a success rate of 96%[37] and another only 26%.[28] Preloading the LMA with a tracheal tube or gum elastic bougie may reduce the failure rate of this technique.[20] An intubating laryngeal mask has been designed and is currently undergoing multicentre clinical studies which may improve the intubation success rate using this principle.

Oesophageal tracheal Combitube

This device (fig. 7) is a double-lumen tube which is passed blindly into the mouth and allows ventilation of the patient's lungs whether the tube enters the trachea or the oesophagus. There are apertures at a supraglottic level from the "tracheal" lumen and a distal opening from the "oesophageal" lumen. There is a small-volume distal cuff and a large-volume pharyngeal cuff. If the tube enters the trachea it can be used in the same way as any tracheal tube and the pharyngeal cuff is redundant. In the majority of cases however, the tube enters the oesophagus, in which case the distal and pharyngeal cuffs are inflated and ventilation is possible via the supraglottic side openings.

The Combitube may have certain advantages over some of the other airway adjuncts available. It requires no instruments for insertion, which makes it useful in difficult situations and locations. It occludes the oesophagus with a distal cuff and allows some "venting" of oesophageal contents via one of the two lumens. It can usually be inserted with the neck in a neutral position, making it potentially useful in trauma patients. Early studies using the device showed improvement in arterial oxygenation compared with tracheal intubation, probably because of a PEEP effect when ventilation is applied through the supraglottic apertures.[23] It has been used successfully during cardiorespiratory arrest by intensive care nurses and paramedics with some success.[9 22 71] Recently, the oesophageal detector device has been used to identify whether the Combitube has been passed into the trachea or oesophagus.[79]

Potential problems include the size of the device; it is more difficult to insert than a laryngeal mask and insertion has not been evaluated formally in the presence of a cervical collar. The technique of insertion requires training and the stomach is inflated if ventilation is applied through the wrong aperture when the device is placed in the oesophagus. Because of its size, significant airway trauma appears to occur in some patients. In recent studies blood has been noted on the Combitube after removal in 24%[46] and 45% (Gabbott, unpublished data) of patients. Airway pressures may also be higher when ventilation is attempted through the side holes. Finally, it has been suggested that ventilation is more effective with the head in a hyper-extended position.[46] This presents a problem when dealing with trauma patients where the neck has to remain in a neutral position. Recent work, however, has demonstrated that the presence of a cervical collar does not appear to significantly impair ventilation (Gabbott, unpublished data).

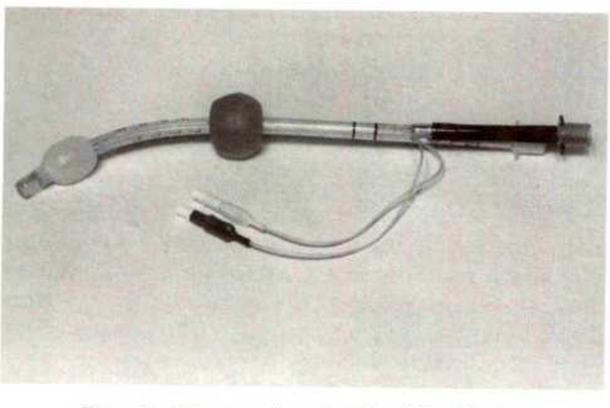

Figure 7 The oesophageal tracheal Combitube.

The Combitube therefore remains an airway adjunct that, in theory, may prove to be useful. Further assessment is required before it can be advocated on a wide scale.

Surgical airway

Resort to the surgical airway is rarely necessary but is a skill that anyone with a claim to expertise in advanced airway management should be able to perform. Direct surgical access to the trachea should be made via the cricothyroid membrane unless there is severe trauma to that region. This involves removal of cricoid pressure, if applied, which makes placement of devices such as the laryngeal mask and Combitube more successful if they are to be used as temporary oxygenation sources. Tracheostomy in the emergency situation is very difficult and probably has no place in advanced airway management during resuscitation.

There are several methods of gaining access to the airway via the cricothyroid membrane, including needle and surgical cricothyroidotomy and blind stab techniques using specifically designed equipment. These methods are hazardous in the emergency situation and should be undertaken when there is no other option and the procedure is life saving. Any of the techniques should be performed only by trained and practised operators. Training is accomplished by the use of manikins, animal larynx specimens, such as those used in the advanced trauma and advanced paediatric life support courses (ATLS and APLS) and by cadaver and post-mortem teaching if these facilities are available.

Needle cricothyroidotomy. This technique, which is the surgical airway of choice for all children because of their small airway size, involves placing a needle and catheter through the cricothyroid membrane and ventilating via a catheter which is left *in situ*. The bigger the catheter the easier is ventilation. However, the technique is only suitable to buy time while a more definitive surgical airway is created. Ventilation is difficult using a self-inflating bag but is more successful when a high pressure source of oxygen is used with inflation intermittently applied by occluding an aperture in the ventilation tubing. Careful observation of chest movement is essential to avoid barotrauma, and for the technique to be safe there should always be a clear route through the larynx and mouth for expired gases to escape. Sufficient expiration through the narrow catheter is usually not possible despite physical attempts to compress the chest.

Surgical cricothyroidotomy. This technique is gaining in popularity, particularly in the trauma setting, although documented evidence of its effectiveness in cardiopulmonary resuscitation is lacking. The procedure involves incision of the cricothyroid membrane under direct vision and insertion of an appropriately sized tracheal tube. Ventilation is highly effective and a secure airway is created.

While surgical cricothyroidotomy appears to be a simple technique, it is not without complications, with some studies reporting a total failure rate of up to 12%.[67] Others, however, have reported a much lower failure rate[55] and this may depend on the skill of the operator. Precautions that can be taken to reduce complications include limiting the lateral extent of any horizontal incision, incising the inferior part of the cricothyroid membrane in an attempt to avoid the cricothyroid arteries, and directing the scalpel blade away from the head to avoid vocal cord damage.

The technique is indicated in cases when life-threatening upper airway obstruction is present and all other attempts to secure the airway and ventilate the patient's lungs have failed. Persistent attempts at tracheal intubation may result in worsening hypoxia and in these cases an early decision to create a surgical airway should be made. Because of the high complication rate significant training and experience are required.

Blind stab techniques. This method uses a single stab technique through the skin, subcutaneous tissues and cricothyroid membrane. Several commercially available kits (Portex, Cook Critical Care, Rusch) allow access to the airway using the technique. Most are simply large trocars over which a short, wide-bore tube is passed with a standard 22-mm connector. Some kits incorporate the use of guide wires and others use a more graded, dilational system.

Whichever product is used it is apparent that the technique may present considerable problems if it is not appropriately taught. Furthermore, access to the airway in the patient who is attempting to breath with a larynx that is constantly moving under the skin can be very difficult. Nevertheless, the concept of a readily available, rapid access device that does not require additional pieces of equipment for insertion is to be commended. Only by using and practising inserting such devices can appropriate experience be gained.

ADVANCED MANAGEMENT OF VENTILATION

Advanced ventilation methods are designed to overcome the shortcomings of expired air resuscitation techniques. However, if applied poorly they can be less effective and more hazardous than well executed basic techniques.

During cardiopulmonary resuscitation oxygenation is paramount; carbon dioxide delivery is likely to be low thus eliminating the requirements for large tidal volumes[11] and lung compliance may be considerably reduced requiring higher inflation pressures.

There is some experimental evidence suggesting that ventilation itself may not be of paramount importance during the first few minutes after cardiac arrest. Indeed chest compression alone may generate sufficient tidal volumes for adequate oxygenation provided the airway is patent and a high inspired oxygen source is provided.[14 72] This may be significant during the first few minutes after cardiac arrest, particularly if first responders are unwilling or unable to provide suitable ventilatory assistance.

Work in humans using active compression–decompression CPR has also demonstrated the potentially satisfactory tidal volumes generated by this technique alone, allowing sufficient ventilation to maintain blood-gas values at near normal levels provided the airway remains patent.[38]

Ventilation devices

Devices for advanced management of ventilation include the self-inflating bag–valve–mask, anaesthesia systems, oxygen powered and automatic resuscitators and devices for transtracheal jet ventilation. These latter devices allow some ventilation via a cannula placed in the cricothyroid membrane, as described above. The system uses a high pressure oxygen source and a purpose designed injector. The method is relatively inefficient at eliminating carbon dioxide, although in cardiac arrest situations this may not be of much importance initially.

The self-inflating bag–valve devices are still the mainstay of ventilation for many during resuscitation. They are portable, robust and convenient but require considerable skill when used with a face mask, and a two-rescuer technique has therefore been recommended.[3 10] The importance of generating large tidal volumes has now been questioned, however, and a single-rescuer technique may be appropriate with smaller lung volumes equally acceptable. Of greater importance is that oxygen is provided at or close to an $F\mathrm{I}_{\mathrm{O}_2}$ of 1.0. This can only be achieved effectively by the use of large volume oxygen reservoir bags or the use of a demand valve.

Anaesthesia systems and manually triggered ventilators have a limited place in resuscitation as they are either in a fixed location or require the operator's hands for providing ventilation, or both. Automatic ventilators, however, give the best all round option; they provide an $F\mathrm{I}_{\mathrm{O}_2}$ of 1.0, consistent tidal volumes and ventilatory frequencies, and free the rescuer's hands for other tasks. Many sophisticated models are now available[57] some of which incorporate air–oxygen mix facilities, the ability to provide PEEP, disconnect alarms, variable I:E ratios and airway pressure monitoring facilities. They are compact, robust and lightweight and function under a variety of climactic and environmental conditions. The only drawback is the relatively large consumption of oxygen that may be used as the driving gas. This may cause problems when no piped gas is available and gas cylinders have to be used.

A flow chart for the advanced management of the airway and ventilation[34] is shown in figure 5.

Acknowledgement

Figures 1–5 are adapted from the Guidelines for basic and advanced management of the airway and ventilation during resuscitation of the European Resuscitation Council and are reproduced with permission. *Resuscitation* 1996; 31: 187–230.

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Advanced life support guidelines

C. E. ROBERTSON

In 1992, the European Resuscitation Council (ERC) published guidelines for advanced life support (ALS). These guidelines were produced by an international group of experts and based on consensus views of the available literature. This European initiative brought together individuals and organizations in a unique endeavour. However, it was recognized that because of the changing nature and incomplete knowledge in the field of cardiopulmonary resuscitation (CPR), that regular review and re-assessment would be required.

In the past 5 yr considerable changes have occurred. Some of the answers to previously unknown and difficult problems, such as the potential value of high-dose catecholamines and use of alternative techniques to increase antegrade blood flow during closed chest compression, are now available. Important new advances have occurred in the technology associated with resuscitation, in particular defibrillation. Manual defibrillators require a level of rhythm recognition and interpretation that many health care professionals find difficult. Semi-automated and automated defibrillators are now widely available, particularly in the pre-hospital environment. The 1992 guidelines were not designed with these devices in mind.

For all of these reasons, a review of the guidelines was both apposite and timely. The formation of the International Liaison Committee on Resuscitation (ILCOR) has facilitated this process by making possible worldwide cooperation and discussion. Representatives from North America, Europe, Southern Africa and Australasia have collaborated to produce the ILCOR advisory statements on resuscitation which were published in April 1997. This article summarizes the ALS component of the advisory statements with particular reference to their use in the UK. The UK, under the aegis of the Resuscitation Council (UK), has accepted the task of assessing these new ALS guidelines on behalf of the ERC under the title "The 1997 Guidelines for use in the UK".

General principles

One of the most difficult tasks of educators is to maintain a consistent and logical approach within the framework of an easily retained message. The limitations of guideline production and use must be acknowledged. Slavish adherence to rigid instructions is rarely practicable or indeed advisable. As often happens in medicine, interpretation with commonsense and an appreciation of intent is necessary.

This is particularly the case in the field of resuscitation where our knowledge is at best incomplete. It is hoped that these guidelines, while offering a clear approach, will also allow individuals with specialist knowledge the opportunity to modify them according to the level of their expertise and the specific clinical situation or environment in which they are used.

The commonest cause of adult sudden cardiac arrest is ischaemic heart disease. The majority of individuals who die from an acute coronary syndrome do so before reaching hospital and emphasis on prevention of cardiac arrest is essential. In relation to this, the correct and timely management of peri-arrest arrhythmias may prevent the development of cardiac arrest[41,41a] (see also page 198).

A small, but important, group of patients develop cardiac arrest in special circumstances; examples include trauma, hypothermia, immersion, drug overdose, anaphylaxis, hypovolaemia, etc. While the ALS guidelines are universally applicable, in these situations specific modifications may be needed to increase the chances of success.

Specific ALS interventions

TRANSTHORACIC DEFIBRILLATION

By far the commonest primary arrhythmia in adult cardiac arrest is ventricular fibrillation (VF).[2,51] In some patients, this is preceded by a short period of ventricular tachycardia (VT) which deteriorates in waveform to VF. Early detection and treatment of these rhythms is central to the chances of successful outcome. The majority of eventual survivors of cardiac arrest come from this group.[21,59] The more rapidly a patient can be defibrillated in these

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COLIN E. ROBERTSON, MB, CHB, MRCP(UK), FRCP, FRCS, FFAEM, Department of Accident and Emergency Medicine, and Surgery, Royal Infirmary, Lauriston Place, Edinburgh EH3 9YW.

circumstances, the greater the chance of obtaining a perfusing cardiac rhythm and the higher the ultimate success rate. It has been estimated that the chances of successful defibrillation decline by approximately 2–7% with each minute that a patient remains in cardiac arrest.[38] This decline reflects rapid depletion of myocardial high energy phosphate stores,[44] and is mirrored in the deterioration of the amplitude and characteristics of the VF waveform.[42] Basic life support (BLS) can slow the rate of decline but does not reverse it. As a consequence, the priority is to reduce the delay between the onset of cardiac arrest and defibrillation.

One of the most interesting developments has been the use of new techniques during defibrillation. These include altering the waveform of the shock, automatically adjusting the energy administered according to transthoracic impedance or producing sequentially overlapping shocks with rapidly shifting electrical vectors.[5 23 32] With most conventional manual defibrillators, the defibrillation waveform used has a damped monophasic sinusoidal pattern. New machines delivering biphasic waveforms can, with lower energies, produce shocks with similar success rates. This technique has the advantage that the inevitable myocardial injury produced by defibrillation is reduced.

An alternative technique is available with some automated defibrillators. These measure the patient's transthoracic impedance immediately before administration of shock and then deliver a shock based on current flow. Current-based defibrillation is particularly useful in patients who have unusually high or low transthoracic impedance values.

Irrespective of the type of machine used, the correct defibrillation technique is important to reduce transthoracic impedance and maximize the chance of success. Only a small proportion of the delivered electrical energy traverses the heart during transthoracic defibrillation so that efforts to maximize this are important. Common faults include inadequate contact of the paddles or self-adhesive pads with the chest wall, failure or inadequate use of couplants to aid current passage between the paddles and chest wall, and faulty paddle positioning or size.[1 3 30 53] One paddle should be placed to the right of the upper part of the sternum below the clavicle, the other just outside the position of the normal cardiac apex (V4–5 position). Placement over the breast tissue in female patients should be avoided to reduce transthoracic impedance. Other positions, such as apex-posterior, can be considered if the standard position is unsuccessful. Polarity of the electrodes appears to influence success with internal implantable defibrillators, but during transthoracic defibrillation the polarity of the paddles is unimportant.

On a practical note, it is important to realize that after administration of a defibrillating shock there is often a delay of a few seconds before an ECG trace of diagnostic quality is obtained. Furthermore, even when a electrical rhythm compatible with cardiac output is obtained after a defibrillating shock, temporary impairment of cardiac contractility is often present and the first few cardiac cycles may be associated with a weak, or difficult to palpate, central pulse. It is important to recognize these phenomena and allow for them rather than concluding that electromechanical dissociation has developed.

CPR TECHNIQUES

Several new experimental techniques have been investigated and evaluated over the past few years; these include simultaneous compression and ventilation, high impulse external chest compression, interposed abdominal compression, vest CPR and active compression/decompression CPR.[15] Some of these techniques have been shown experimentally to improve the haemodynamic state associated with CPR and in some cases to improve survival in animal models. It is disappointing that at present there are no clinical data showing unequivocal improvement in outcome in large-scale human studies with any of these techniques.[50 56] Consequently, the new guidelines do not recommend any change in the technique of closed chest compression.

AIRWAY MANAGEMENT AND VENTILATION

In 1996, an ERC working group published guidelines for the advanced management of the airway and ventilation during CPR.[6] These are incorporated into the advanced life support guidelines and their detailed aspects are covered separately in this issue of the journal.

After cardiac arrest and during CPR, normal pulmonary physiological characteristics are altered. There is an increase in deadspace and a reduction in lung compliance because of the development of pulmonary oedema. These changes may compromise gas exchange and serve to focus attention on the delivery of oxygenation and ventilation of the patient's lungs. The aim should be to provide a fractional inspired oxygen concentration ($F\text{I}_{\text{O}_2}$) of 1.0. Fortuitously, carbon dioxide production and its delivery to the pulmonary circulation is limited by the relatively low cardiac output achieved during CPR. As a consequence, high tidal volumes are unnecessary to achieve adequate carbon dioxide excretion and the prevention of hypercapnia. This situation may, however, require some modification if carbon dioxide producing buffers are administered (see below) and relative increases in minute ventilation are required to prevent carbon dioxide build-up and the development of hypercapnic acidosis.

DRUG DELIVERY DURING CPR

The optimal method of drug administration during CPR is still the pervenous route.[24] Central venous cannulae can deliver drugs rapidly and efficiently to the central circulation. In general, provided cardiac arrest has not ensued as a consequence of hypovolaemia, the central veins are often full; nevertheless, central venous cannulation by whatever route (e.g. internal jugular or subclavian) requires considerable technical proficiency. The risks associated with the technique of central cannula insertion are significant. Well recognized complications include pneumothorax (with the possibility of the development of tension), arterial puncture, air embolus and catheter malposition. Some of these can be life threatening and early detection may be difficult. Obviously, if a central venous cannula is already *in situ*, it should be used. Otherwise, for an individual patient, the decision to attempt central venous cannulation depends on the skill of the operator, available equipment, nature of the surrounding events and time scale. If the decision is made to perform central venous cannulation it must never delay defibrillation attempts, performance of CPR or security of the airway.

Where a peripheral venous route is used, a flush of 20–50 ml of 0.9% saline is given after drug administration to expedite entry to the central circulation. Administration of drugs by the tracheal route is theoretically attractive, particularly if there is no immediate access to the systemic circulation. During the management of cardiac arrest, tracheal intubation frequently precedes venous cannulation, particularly in patients where venous access is rendered difficult by obesity or previous drug use. Unfortunately, the early promise shown by tracheal drug administration has not been confirmed. Impaired absorption and unpredictable pharmacodynamics means that drug administration by this route remains a second line approach.

Drugs which can be given by this route are also limited, currently to adrenaline, lignocaine and atropine. It is recommended that doses of 2–3 times the standard i.v. dose are given, diluted up to a total volume of at least 10 ml in 0.9% saline. After administration, five ventilations are given in an attempt to maximize absorption from the distal bronchial tree. Theoretically, administration of the agent by deep endobronchial application would be advantageous. This would necessitate the use of a catheter inserted via the tracheal tube. Surprisingly, for lignocaine, no advantage was demonstrated from deep endobronchial administration.

DRUG THERAPY DURING CPR

Over 100 yr ago, adrenaline was used to produce peripheral vasoconstriction and re-start the hearts of animals in asystole. For the past 40 yr adrenergic agents have been advocated as the mainstay of pharmacological therapy in cardiac arrest. There is no doubt that experimentally adrenaline (and other adrenergic agonists) can improve myocardial and cerebral blood flow.[45] In animal studies this can result in improved resuscitation success rates. These effects are dose-dependent and higher doses are more effective than the "standard" dose of 1 mg. Unfortunately, the human clinical experience is much less clearcut. There is little evidence that adrenaline unequivocally improves survival or neurological recovery rates in humans after cardiac arrest.[26, 62] Although slightly increased rates of spontaneous circulation have been seen in some clinical studies with high-dose adrenaline, there was no overall improvement in survival rate.[7, 10, 40, 55]

It is interesting to conjecture why there are these marked differences between experimental and clinical results. They may in part reflect the differences in underlying pathology between the human and animal heart, together with the relatively long periods of cardiac arrest before ALS procedures enable adrenaline to be given in the clinical setting. Furthermore, it is possible that higher doses of adrenaline could be counter-productive in the post-resuscitation period by increasing myocardial oxygen consumption, adversely affecting patterns of endocardial, epicardial and pulmonary blood flows, and inducing the pattern of myocardial injury known as contraction band necrosis.[46, 58]

To date, there has been no randomized, controlled study in humans comparing standard dose adrenaline (1 mg every 3 min) with placebo of sufficient power to provide an unequivocal result. Pending this, it is recommended that the indication, dose and time intervals between doses of adrenaline remain unchanged.

The risks of routinely administering adrenaline to patients in whom cardiac arrest is provoked by, or associated with, solvent abuse, cocaine and other sympathomimetic drugs should also be remembered.[37, 39, 52]

The use of antiarrhythmic agents to prevent arrhythmias is well established. Their use to facilitate defibrillation is, however, much less clear. There is no doubt that animal models have dramatically improved our knowledge of the mechanisms of arrhythmogenesis and antiarrhythmic drug actions.[4] As with adrenaline, however, extrapolation from the animal to the clinical model is fraught with problems.

Of all the antiarrhythmic agents used in cardiac arrest, we know more about lignocaine than any other drug. Initial concerns that lignocaine increased the ventricular defibrillation threshold are probably more related to the experimental technique than an effect of the drug.[13, 17, 20, 31, 43] In humans, the energy requirements for defibrillation were not increased when lignocaine was given.[36] Whether lignocaine was more efficacious than other agents, such as bretylium, is unknown. The CALIBRE study, a multicentre study which is currently evaluating these two agents in this situation, is now underway. Pending this, it is recommended that no change be made in relation to previous recommendations on the use of lignocaine, bretylium or other antiarrhythmic agents.

The use of atropine in the treatment of haemodynamically compromising bradyarrhythmias and some forms of heart block is well established.[41] Atropine has previously been advocated in the management of asystole on the basis that an increase in vagal tone could produce arrhythmias or reduce the potential efficacy of other therapies in re-starting an electrical rhythm.[61] Evidence of efficacy of atropine in asystole is limited to small series and case reports.[8, 16, 25, 57] Nevertheless, the prognosis of asystolic states is so poor and the likelihood of significant adverse effects produced by atropine so limited, that its use in this situation can be considered. In healthy human volunteers, a single dose of 3 mg i.v. is sufficient to block vagal activity completely and this dose is recommended if atropine is considered for asystole.[12]

Provided that effective basic life support is performed, arterial blood-gas analysis shows neither rapid nor severe development of acidosis during cardiorespiratory arrest in previously healthy individuals.[25,54] Arterial blood-gas analysis is commonly performed to assess acid–base status, but alone may be misleading. Even co-terminously measuring arterial and mixed central venous blood-gas samples may be of little value in estimating the internal milieu of myocardial and cerebral intracellular acid–base status.[11,29,34,60]

In the past, administration of sodium bicarbonate as a buffer was advised to reverse the potentially deleterious effects of acidosis. Potential adverse effects of sodium bicarbonate administration include alkalaemia, hyperosmolarity and carbon dioxide production. Other agents, such as sodium carbonate, Carbicarb (a mixture of sodium carbonate and sodium bicarbonate), tromethamine (THAM) and tribonate (a mixture of sodium bicarbonate, THAM, phosphate and acetate) have been suggested to minimize some of these effects.[22] However, there is no clinical evidence to suggest that carbon dioxide consuming buffers, or indeed any buffer, are effective in increasing survival rates after human cardiac arrest.[19,33,35] The best method of reversing acidosis associated with cardiac arrest is to restore spontaneous circulation. At present, in the UK, sodium bicarbonate remains the buffer of choice. It is suggested that its judicious use is limited to patients with severe acidosis (arterial pH less than 7.1 and base deficit less than −10) and to cardiac arrest occurring in special circumstances, such as hyperkalaemia or tricyclic antidepressant overdose.

The universal ALS algorithm

There is now a single algorithm for ALS management; it is applicable for health care providers using manual, semi-automatic or automatic defibrillators (fig. 1). Each step of the algorithm presupposes that the one before has been unsuccessful.

The route of access to the ALS algorithm depends primarily on the events surrounding the cardiac arrest. In many situations, such as out-of-hospital cardiac arrest, basic life support will already have been started. This must continue while the monitor/defibrillator is being attached. In patients who are already monitored, clinical and electrocardiographic detection of cardiac arrest should be nearly simultaneous. In these situations, patients who have had a witnessed collapse can have a single precordial thump administered pending attachment of the monitor/defibrillator or if there is any delay in administration of the first defibrillating shock.[9,47]

Analysis of the ECG rhythm must take place within the clinical context. Movement artefact, lead disconnection and electrical interference can all mimic cardiac arrest rhythms. For the rescuer with a manual defibrillator, the crucial decision is whether or not the rhythm present is VF/VT. If VF/VT is suspected, defibrillation must occur without delay. The first shock is given with an energy level of 200 J for a standard monophasic shock, or its equivalent if a biphasic waveform in used. If the first defibrillating shock is unsuccessful, a shock of the same energy (200 J) is repeated. If still unsuccessful a third shock is given, this time at 360 J.

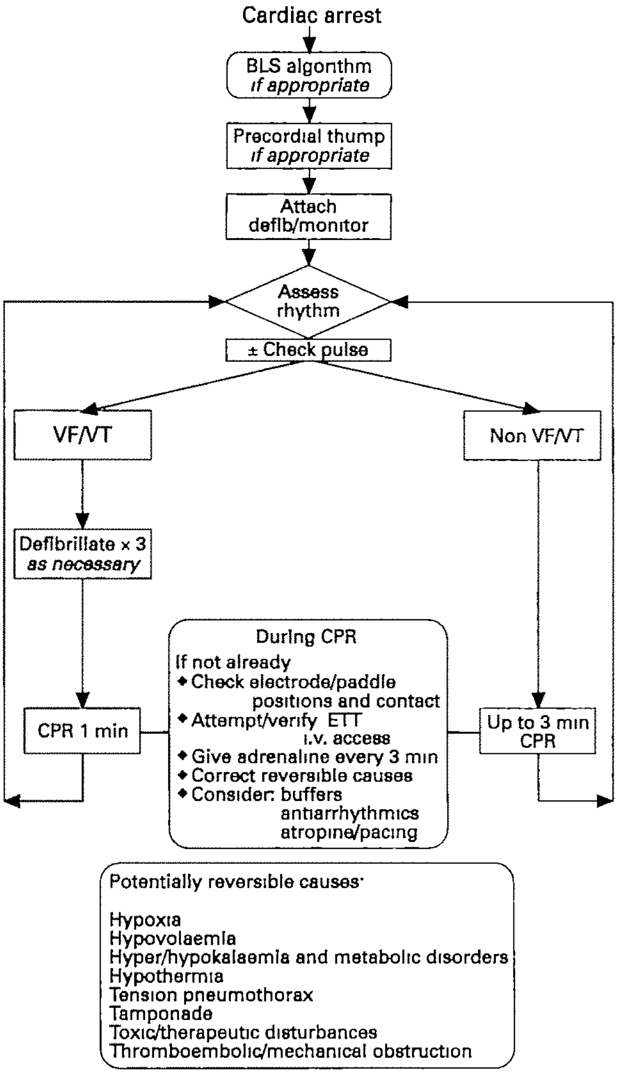

Figure 1 Algorithm for advanced life support management. BLS=Basic life support

A check of a major pulse is performed if, after a defibrillating shock, an ECG rhythm compatible with cardiac output is obtained. If, however, the monitor/defibrillator indicates that VF persists, then the additional shocks in the sequence of three can be administered without a further pulse check.

With modern monitor/defibrillators it is possible, if necessary, to administer the first three shocks within a period of 60 s, and in the majority of patients who are treated successfully, defibrillation occurs after one of the first three shocks. If the first sequence of three shocks is unsuccessful, the best chance for restoring a perfusing rhythm is still defibrillation but correction of reversible causes or aggravating factors, and attempts to maintain myocardial and cerebral perfusion and viability, are indicated at this stage.

Potential causes or aggravating factors leading to persistent VF/VT may include electrolyte imbalance, hypothermia and drugs or toxic agents for which specific therapy may be required (see fig. 1). These interventions, together with checking defibrillating paddle/electrode positions and contacts, should occur during the 1-min period of CPR.

During this time, attempts are made to secure advanced airway management and ventilation and to institute venous access. The first dose of adrenaline is given.

It is unlikely that even with a highly trained team all of these aspects will be completed within this first CPR interval, but further opportunity will occur with the next cycle.

The ECG rhythm is then re-assessed. If VF is still present, the next sequence of defibrillating shocks is started without delay. These shocks are all at 360 J (or equivalent).

Provided that resuscitation was started appropriately, sequential loops of the left-hand side of the algorithm are continued, allowing further sequences of defibrillating shocks, CPR and the ability to perform/secure advanced airway and ventilation techniques and drug delivery. As long as resuscitation has been started appropriately, it should not normally be abandoned while the ECG rhythm is still recognizably VF/VT.

If at the time of initial rhythm analysis, VF/VT can be positively excluded, clearly defibrillation is not appropriate. In this situation, the right-hand side of the algorithm is followed. These patients may have asystole or electromechanical dissociation (EMD). Any electrical rhythm associated with cardiac arrest will, if untreated, deteriorate to asystole. The prognosis for these rhythms is, in general, much less favourable[14,27] but nevertheless there are some situations where they have been provoked by remediable conditions which, if detected and treated promptly, may lead to success. The common causes are listed in figure 1 and may be recalled under the headings of the 5 H's and 4 T's.

Cardiac pacing may be of value in patients with extreme bradyarrhythmia. Its efficacy in true asystole is unproved, except in cases of trifascicular block where p waves are present. If pacing is contemplated and delay occurs before its institution, external cardiac percussion (fist pacing) may be effective in producing cardiac output, particularly in those situations where myocardial contractility has not been critically compromised.[18,48,49] While the search for, and correction of, these potential causes of arrest are underway, basic life support with advanced airway management and ventilation, venous access, etc, should occur as before, and adrenaline is administered every 3 min.

After 3 min of CPR, the ECG rhythm is re-assessed. If VF/VT has developed, then the left-hand side of the algorithm is followed. If a non-VF/VT rhythm still persists, loops of the right-hand side of the algorithm continue for as long as is considered appropriate for resuscitation to continue.

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Paediatric and neonatal life support

D. A. ZIDEMAN

Resuscitation of infants and children is different from adult resuscitation. Although there may be many similarities in the methodologies used in the resuscitation procedures with those used in adults, paediatric life support is governed by the fact that it begins from a different starting point. Adult sequences are based on the observation that the majority of cases are primarily cardiac in origin; arrest is therefore rapid and immediate in onset giving little or no warning of occurrence and usually requiring rapid defibrillation to achieve any measure of success. In infants and children the cause is usually primarily a respiratory event which leads to the final cardiac arrest if not recognized and dealt with promptly.[43 46 95 96 105] Primary cardiac arrest in children is rare and ventricular fibrillation and ventricular tachycardia have been reported in less than 15% of the young.[4 40 64] The aetiology and pathogenesis of sudden death in this age group is therefore important. Many children have a relatively long "pre-arrest" phase, cardiac arrest signalling the end of a progressive physiological decline. It could be argued that in such events many deaths could be prevented by early recognition and aggressive therapy in this "pre-arrest" phase but, unfortunately, some remain irreversible despite all efforts.

Trauma is the one cause of cardiac arrest that occurs in both children and adults and is the most common cause of death in the first four decades of life. It could be argued that trauma is preventable and, more importantly, cardiac arrest secondary to trauma can in some cases be prevented by careful correct management of the airway, breathing and circulation of the trauma victim before managing the secondary injuries.

The outcome of paediatric life support is disappointingly low with survival rates between 3 and 17%.[23 25 32 43 46 57 64 71 82 90 98 105] These poor survival results are even more dismal when the majority show significant neurological impairment after arrest. The variability in results is attributed to whether the primary event was respiratory in nature, which has a better outcome,[25 55 98] or a primary cardiac event, which has a worse prognosis.[25 32 72] Furthermore, events occurring outside hospital[25 31 32 57 68 72 84 96 98 99] have a poorer outcome than those occurring in hospital.[22 24 32 34 55 58 72 104 105] Audit and analysis of paediatric life support events are complex. Resuscitation is relatively uncommon and many studies have collected data for several years and still have small sample sizes. In the BRESUS study in the UK, only 2% of victims were aged less than 14 yr.[100] In an American study surveying 15 yr of prehospital events, only 7% of victims were less than 30 yr of age and 3.7% were less than 8 yr old.[4] Furthermore, definitions used in evaluating events are inconsistent and often not comparable from study to study. In an effort to improve our knowledge of paediatric life support and its outcome, a revised reporting template was formulated. It is hoped that these paediatric Utstein style guidelines[106] will help to standardize the reporting of outcomes of paediatric life support and thereby provide an evidence-based practice of comparable data sets to establish the true worth of these events.

One conclusion is clear; infants and children who progress to cardiac arrest have a very poor prognosis. Because of the aetiology of resuscitation in these age groups it is important that the pre-event symptoms are recognized early and treated effectively before respiratory collapse and the inevitable cardiac arrest. Therefore, in paediatric life support, prevention and early recognition of the impending event are major factors for overall survival.

Paediatric life support

Guidelines for paediatric life support have been published by several national organizations.[1 26 51 73 87] In 1992, an International Liaison Group was established to examine the basic scientific data, analyse national differences and formulate recommendations based on science which would form the basis of international guidelines to be used in the future by individual national organizations. In 1997 the International Liaison Committee on Resuscitation (ILCOR), a multi-national committee comprised of members representing most of the major national resuscitation organizations, published a series of advisory statements, including a paediatric statement.[47] In paediatric life support the committee found very few areas of serious controversy. It is

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Key words

Complications, cardiac arrest. Heart, resuscitation. Children. Infants.

D. A. ZIDEMAN, QHP(C), BSC, MBBS, FRCA, DIPIMC, Department of Anaesthesia, Hammersmith Hospital, Du Cane Road, London W12 ONN.

hoped that the paediatric ILCOR advisory statement will form the foundation to build national procedures and to highlight areas which need further scientific investigation and research.

Age definitions

Paediatric life support deals with the resuscitation of infants and children. Because of the wide variation in anatomy, physiology and epidemiology throughout the paediatric age range, it is therefore important to define various age ranges in an effort to rationalize treatment.

ANATOMY

The size of a child is an obvious important consideration in determining the practical resuscitation procedure to be followed. Two categories are suggested: (1) infants less than 1 yr of age; and (2) children aged 1–8 yr.

The upper age limit of 8 yr for children has been proposed as a watershed, particularly in relation to the technique of chest compression. A small child less than 8 yr of age probably receives adequate chest compressions using a "one-handed" technique. An older or larger child probably requires a "two-handed" (adult) technique to achieve adequate depth of compression. None the less, because of the variability in size of children, no definitive upper age limit can be set and the rescuer must judge the effectiveness of the resuscitation and adapt the technique appropriately.

PHYSIOLOGY

From a physiological point of view it could be suggested that the upper age limit should be puberty. Although this has been considered carefully, evidence has shown that the physiological changes of puberty have little effect on paediatric life support. In the newborn the physiological differences are obvious; the non-compliant newborn lungs require a unique sequence of resuscitation procedures, which although superficially still follow the same "ABC" sequence, require the development of a different practice.

EPIDEMIOLOGY

Much has already been written on the differences in resuscitation epidemiology between adults and children. Considering the epidemiology, it could be suggested that older children, adolescents and young adults have the same underlying causes of collapse and arrest which are more aligned to paediatric than adult procedures. In the newborn it is important to establish the first breath and maintain effective ventilation and oxygenation. In the infant and child, airway and breathing problems predominate and lead rapidly to bradycardia and asystolic cardiac arrest. Primary cardiac events should be considered only when there is a pre-existing history of heart disease. The conclusion is simple; the resuscitation sequence must be determined by the most likely cause of the event. The common aims of all forms of paediatric life support are establishment of a clear airway and oxygenation of the lungs; these are prerequisite to all other forms of treatment.

Basic life support (fig. 1)

ASSESS RESPONSIVENESS

Before starting a resuscitation procedure it is vital to evaluate the situation for any danger or physical hazards. The first step is to assess the level of responsiveness. Gentle but firm stimulation must be given and this alone may be sufficient to awaken the child or stimulate respiration. Infants should not be shaken vigorously nor children with a suspected spinal injury. If the child is unresponsive, shout for help. Only move the child if he is in a dangerous location.

AIRWAY

The tongue is the most common cause of airway obstruction in children.[88] Simple head tilt–chin lift or jaw thrust manoeuvres establish the paediatric

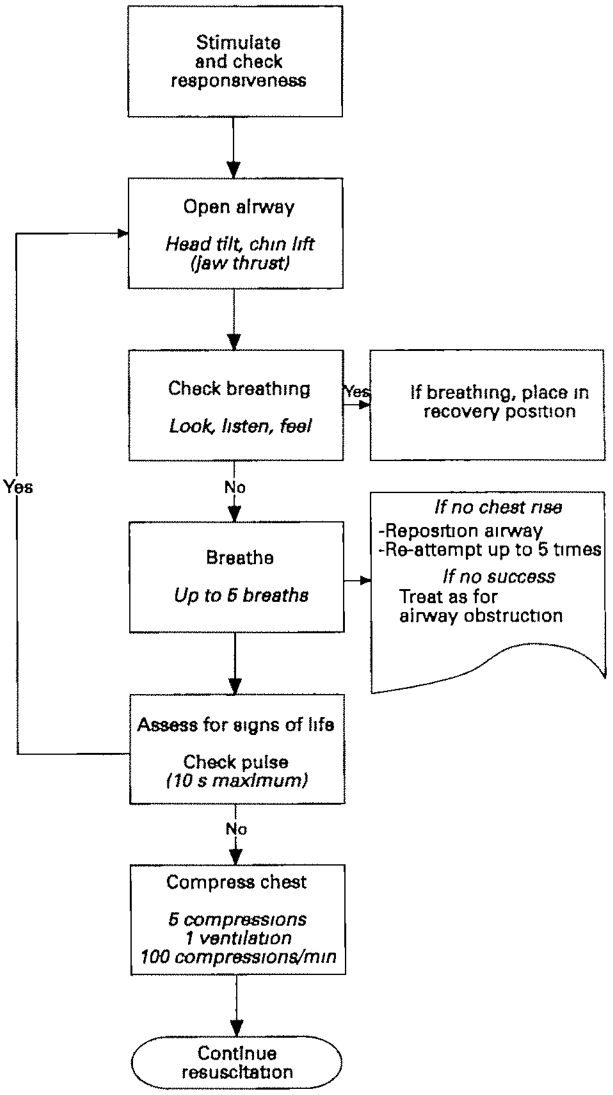

Figure 1 Algorithm for paediatric basic life support.

airway; only the jaw thrust procedure is recommended when trauma is the cause of collapse. More recently, a tongue–jaw lift manoeuvre has been described accompanied by visual inspection of the mouth,[86] but further evaluation has yet to establish the value of this procedure.

If a foreign body is obstructing the airway it should be removed carefully under direct vision. Blind probing of the child's airway is likely to impact the object further or to cause tissue damage, and should be discouraged. Where complete upper airway obstruction has occurred as a result of inhalation of a foreign body, the object is probably too far into the airway to be seen or removed by simple means and advanced airway procedures are needed.

BREATHING

Assessing effective breathing is very difficult[6] and subject to errors. Three methods are recommended in assessing respiration.

(1) Look for chest and abdominal movement.

This detects physical movement, but it may not be coordinated and effective to move air in and out of the lungs.

(2) Feel at mouth and nose for air movement.

This confirms the effectiveness of the chest movement.

(3) Listen over the airway for breath sounds.

An important manoeuvre which indicates if the child has large or small airway problems. Absence or lessening of airway noise could mean that the problem is improving; alternatively, it could indicate that the child is moving less air past the obstruction and that the situation is getting worse.

If the infant or child is not breathing, it is essential to commence expired air ventilation immediately. The mouth of the rescuer applied to the mouth and nose of the infant has been the conventional teaching, but recently the effectiveness of the mouth of the rescuer applied to the nose of the infant has been described.[91 97] In the child, mouth-to-mouth expired air ventilation is recommended. A minimum of two but up to five breaths may be required. In some situations two breaths may be sufficient to re-establish signs of life and spontaneous respiration. Because of the probable hypoxic aetiology of the event, five breaths are considered the optimal number of breaths to oxygenate a child. The breaths should be slow, each lasting 1–1.5 s. These slow breaths minimize gastric distension from high-pressure, high-flow ventilation.[62 63] It is also important not to ventilate with excessive tidal volumes as this may lead to gastric distension and regurgitation of gastric contents.[11] A simple and effective guideline is to observe the child's chest and to stop ventilation when the chest rises to the equivalent of a deep breath. If the chest does not rise when attempting ventilation, realign the airway (over extension of the neck may occlude the airway) or consider clearing the airway using the procedures described in "foreign body airway obstruction" below.

CIRCULATION

Assessment of the circulation at this point in the resuscitation sequence has conventionally been by checking the pulse. Assessment of the brachial pulse is recommended in infants[17] and assessment of the carotid pulse in children. Alternatively, the femoral artery can be palpated. Despite its apparent simplicity the lay rescuer and even experienced health care providers have difficulty in performing the pulse check accurately[12 60 65 66] and the value of the pulse check during resuscitation has been questioned. For example, if an unresponsive infant does not show obvious signs of recovery after expired air ventilation is there any point in delaying chest compressions for a pulse check? The concept of not performing a pulse check before commencing chest compressions is difficult and it may appear illogical not to formally establish cardiac arrest before commencing chest compressions.

The current recommendations cover the difficulty in making an accurate pulse check by stating that if a pulse is not confidently detected within 10 s, further resuscitation interventions should not be delayed. Furthermore, in the infant, if the pulse rate is slow (less than $1\ s^{-1}$ or $60\ min^{-1}$), cardiac output should be considered to be ineffective and full resuscitation commenced.

CHEST COMPRESSIONS

Chest compressions are performed on the lower half of the sternum. In the infant, compression is performed using two fingers placed 1 finger's breadth below an imaginary line joining the nipples. In the child, the heel of one hand is used and positioned 1 finger's breadth up from the xiphisternum. In the older child (more than 8 yr of age) and in the larger young child, this one-handed compression technique may be found to be inadequate and the two-handed compression technique (as used in adult resuscitation) may be required to produce effective chest compression.

The depth of compression should be judged in relative rather than absolute terms. For infants and small children it is recommended to compress the chest to one-third of its resting diameter. The efficacy of chest compression can be judged by palpation of the femoral vessels but this may reflect venous and not arterial blood pulsation.[8] More effective assessment can be made by analysis of the arterial waveform or evaluation of the expired carbon dioxide tracing.

The compression rate is 100 compressions per minute. A single expired air ventilation should be given after every five compressions. This provides adequate ventilation and oxygenation for the infant or child. In the older child, where two hands are required for effective chest compression, the adult ratio of 15 compressions to two ventilations can be used, compressing the chest at a rate of 100 per minute.

Activation of the emergency medical services

Ideally, the call for help given during the assessment of responsiveness should have activated the emergency medical services. In reality this is not always the case, and the priority in paediatric life support is to establish an airway, commence effective breathing and circulate oxygenated blood. In paediatric life support therefore, resuscitation is started and the emergency medical services activated after approximately 1 min of resuscitation. Thus paediatric procedures have adapted the "phone fast" rather than "phone first" philosophy based on aetiological considerations of the resuscitation event. This is a general recommendation but local emergency medical services' circumstances or the availability of "dispatcher-guided CPR" may override these recommendations.

Basic life support must continue without further interruption until experienced help arrives or until signs of life return.

Foreign body airway obstruction

Aspiration of food or vomit, or inhalation of a foreign body compromises the paediatric airway. Spontaneous coughing to clear the material should be encouraged but if this fails, back blows and chest thrusts in infants and back blows together with alternate cycles of chest thrusts and abdominal thrusts in children may provide sufficient vibration to loosen the material and enough expiratory force to expel the obstruction. Abdominal thrusts are not recommended in infants less than 1 yr of age as damage to the abdominal contents may occur. The importance of checking the mouth, formally opening the airway and attempting expired air ventilation after each cycle has been highlighted by the need to assess constantly that the airway is actually obstructed. These checks are also required to assess if the clearing manoeuvres have dislodged the material sufficiently to allow air pass the obstruction. The precise sequence for relief of airway obstruction has not been assessed formally.

Advanced life support (fig. 2)

Basic life support in an essential prerequisite to the paediatric life support sequence. Advanced life support provides the definitive management of the various resuscitation modalities in the hope of restoring spontaneous cardiac activity. Unlike adult resuscitation, the paediatric procedure emphasizes the importance of the airway and oxygenation. Furthermore, the paediatric procedures regard asystole as the primary arrythmia; ventricular fibrillation has been documented in less than 10% of paediatric arrest calls,[4,23,25,34,103] even when the cardiac rhythm is assessed within 6 min of activation of the emergency medical services.[57,64]

AIRWAY

The simple basic procedures of head tilt, chin lift or jaw thrust remain the mainstay of airway management. Insertion of an oropharyngeal airway, correctly sized from the centre of the mouth to the angle of jaw, may be of use to aid simple airway control in the short term.

Tracheal intubation is the most effective method of securing the paediatric airway. Using a straight bladed laryngoscope and a plain plastic tracheal tube of the appropriate size (internal diameter (mm)=(age in years/4)+4) is a technique which requires a skill only developed by formal training and regular practice. Intubation must be achieved rapidly and accurately without prolonged delay to basic life support. Any attempt lasting longer than 30 s should be abandoned and the child's lungs reoxygenated before another attempt is made. Having achieved tracheal intubation the tube needs to be fixed carefully in place to prevent accidental removal or displacement.

The laryngeal mask airway has been assessed as an effective airway adjunct in adult resuscitation and is a technique that can be taught easily to doctors, nurses and paramedic staff.[2,20,21,59,75,89] Small-sized laryngeal masks are available for infants and children but their effectiveness in paediatric resuscitation has yet to be established. They are probably most significant where intubation is difficult or where the health care provider is not proficient in paediatric tracheal intubation.

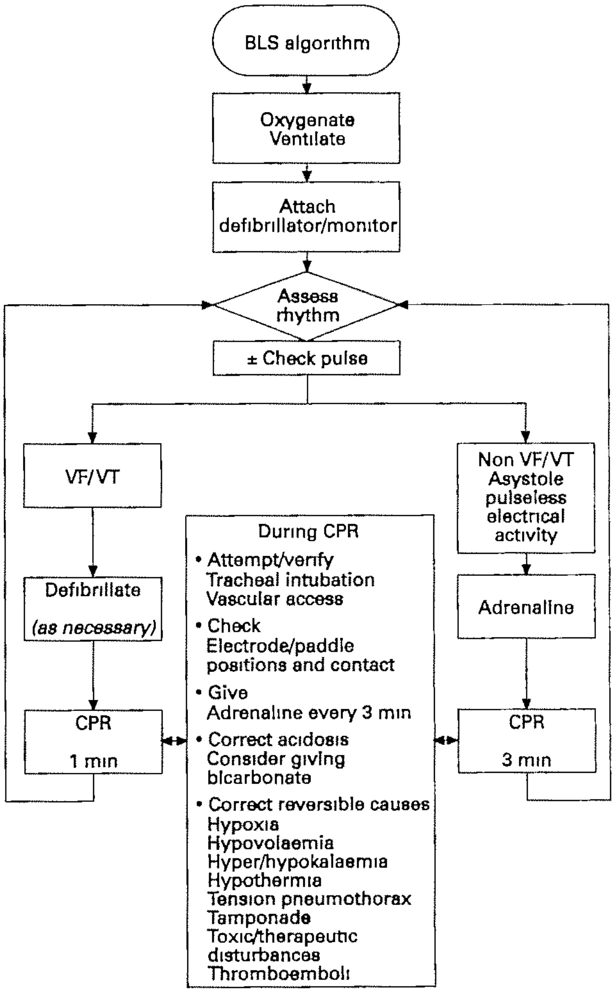

Figure 2 Algorithm for paediatric advanced life support. BLS=Basic life support.

OXYGENATION

Although expired air resuscitation provides some oxygenation, the sooner ventilation with high inspired oxygen concentrations can be established the better. Ventilation using a self-inflating bag–valve–mask with supplementary oxygen provides higher concentrations of inspired oxygen. Concentrations of up to 90% may be achieved if the self-inflating bag is fitted with an oxygen reservoir system. Face masks for use with a self-inflating bag should be of clear plastic so that the airway can be observed through the mask, and the circular design mask with a soft seal rim has been found to be most efficient, especially for the inexperienced operator.

Although many anaesthetists are experienced in the use of the Ayre's T-piece with the Jackson–Rees modification for paediatric ventilation, this system is not recommended for the less experienced and should not be part of the routine resuscitation equipment. Furthermore, this system requires a constant reliable gas delivery system to be functional and this may not always be immediately available. The self-inflating resuscitation bag can function independently and has the advantage that it can be operated safely and effectively by less experienced operators.

CIRCULATION

There are few procedures more fraught with difficulty in resuscitation than the establishment of venous access in an infant or small child during resuscitation. Yet circulatory access is of prime importance to effective advanced life support.[14,49] The i.v. or intraosseous routes for drug delivery are the preferred options. The site of venous access has to be balanced against the resuscitation skills and relative difficulty and risks of the technique. Experimental data have demonstrated that vascular access draining into the superior vena cava from either peripheral or central routes is preferable during resuscitation.[19,27,83] Drugs given via the inferior vena cava take longer to reach the heart.[27,83] Similarly, drugs administered centrally act more rapidly than those administered via the peripheral route.[5,27,41,53] However, access above the diaphragm is difficult and fraught with potential problems. Peripheral access, especially via veins in the lower limbs, is usually easier during resuscitation. Drugs administered via the peripheral route should be followed by a fluid flush to move them rapidly into the circulation.[28] Therefore, when judging the advantages of different access points and deciding which to select it must be remembered that accuracy, safety and speed are the key priorities.

Intraosseous access has gained popularity in the past few years. It is relatively easy to perform and generally safe. Resuscitation drugs and fluids administered by this route reach the heart in a time comparable with direct peripheral venous access.[3,70,85,102] Although originally recommended for children less than 6 yr of age, the intraosseous route has been used in older age groups and in adults during cardiac resuscitation.[35,102] When establishing intraosseous access it is important to recognize the criteria for successful entry into the bone marrow. There should be loss of resistance as the marrow cavity is entered, the needle should remain upright without support, bone marrow should be aspirated into a syringe and there should be free flow of drugs and fluid without subcutaneous infiltration around the entry point.[7,30,94] Marrow aspirates can be used for estimation of concentrations of haemoglobin, sodium, potassium, chloride and glucose.[101] Almost all drugs and infusions can be administered via the intraosseous route except bretylium tosylate,[80] but this drug is rarely administered to children. Complications of intraosseous cannulation include osteomyelitis, long bone fractures, extravasation of drugs subcutaneously and compartmental syndrome.[18,33,42,54,67,76,79,85,92]

The tracheal route of administration of drugs is preferred after the i.v. and intraosseous routes. It is best used where there has been, or is likely to be, a significant delay in establishing venous access and thus administration of drugs. Therefore, during resuscitation of the small infant or child it could be argued that the first important dose of adrenaline should be given by the tracheal route while venous access is being established.[38,56] There has been little research on the efficacy of drugs administered via the tracheal route in children. The optimal dose of drug, its volume and concentration have yet to be established.[48,61,77,81] Tracheal administration, despite its apparent simplicity, has some disadvantages, especially in the post-resuscitation period. Hypertension and tachycardia, neither of which are optimal in the post-arrest myocardium, have been reported and attributed to the depot storage effect of adrenaline which occurs in the lungs.[39,44,45,69,78] Severe hypertension may also be an underlying cause for poor cerebral outcome.[10]

Although direct intracardiac injection still has its advocates, it is now regarded as a last resort, only to be used when all other methods have failed.

TREATMENT ALGORITHMS

Administration of adrenaline plays a pivotal role in the advanced life support algorithms of paediatric resuscitation. Adrenaline is the drug of choice in any paediatric event as, by its alpha adrenergic action, it increases aortic diastolic filling pressure and thereby improves coronary perfusion.[52,71] Establishing venous access and ventilating with oxygen are the first steps in advanced life support and form the basis for the advanced treatment procedure. The algorithm then divides into two pathways according to the underlying cardiac rhythm—non-ventricular fibrillation (or tachycardia) or ventricular fibrillation (or tachycardia).

Non-ventricular fibrillation or tachycardia

Profound bradycardia or asystole is the most common rhythm associated with cardiac arrest in infants and children. Profound bradycardia (usually described as a pulse less than 1 beat s^{-1}) may precede asystole but in itself bradycardia does not produce adequate cardiac output in children.

Profound bradycardia should therefore be treated in the same way as asystole. Treatment is an initial dose of adrenaline 10 $\mu g\ kg^{-1}$ i.v. or by the intraosseous route (or 10 times this dose via a tracheal tube if venous access has not been established) (10 $\mu g\ kg^{-1}$ is 0.01 $mg\ kg^{-1}$ or 0.1 $ml\ kg^{-1}$ of a 1:10 000 solution). Recent studies in animals[9,13,36,85] and children[74] have suggested the benefit of a higher dose of adrenaline for the unresponsive asystolic child. Therefore, should the child not respond to the initial dose, another dose of 100 $\mu g\ kg^{-1}$ (0.1 $mg\ kg^{-1}$ or 0.1 $ml\ kg^{-1}$ of a 1:1000 solution) is recommended. Further studies have shown that if the child does not respond to this higher dose the eventual outcome is likely to be poor.[23,90,105] In reviewing the results of these studies, no children survived to discharge of those given more than two doses of adrenaline. The algorithm may therefore be self-limiting but there is not enough evidence at present to recommend limitation of the time course of resuscitation from non-ventricular fibrillation.

Where there is a cardiac rhythm but no cardiac output (electromechanical dissociation/pulseless electrical activity) it is also necessary to treat any of the underlying reversible causes of the arrest. Hypoxia, hypovolaemia, tension pneumothorax, cardiac tamponade, drug overdose, hypothermia and electrolyte imbalance are all treatable, and resuscitation attempts should not be abandoned until a reasonable attempt has been made to correct these potentially reversible causes of cardiac arrest.

Ventricular fibrillation and tachycardia

These rhythms, although common in adults, are relatively rare in infants and children. Although one study[32] reported an incidence of ventricular fibrillation of 23% in children, most other studies have reported an incidence of 0–10%.[25,3,57,68,98] None the less, the physician must always be aware of the occasional need to treat ventricular fibrillation in children by defibrillation.

The recommended sequence is to give two rapid defibrillatory shocks of 2 $J\ kg^{-1}$, followed by a single shock at 4 $J\ kg^{-1}$. All further defibrillation attempts should then be made at 4 $J\ kg^{-1}$ in a rapid repeated series of three shocks. After the first cycle of three defibrillation attempts adrenaline 10 $\mu g\ kg^{-1}$ should be given and another dose of 100 $\mu g\ kg^{-1}$ after the second cycle of three shocks and between all subsequent cycles. When ventricular fibrillation occurs in children there is often an underlying cause and correction of hypothermia, drug overdose (tricyclic antidepressant overdose) and electrolyte imbalance (hyperkalaemia) should be considered.

Resuscitation of the newborn (fig. 3)

Despite the fact that most newborn infants breathe spontaneously after delivery, it has been estimated that 900 000 infants per year worldwide could be saved from newborn asphyxia by the use of simple airway manoeuvres. Of the 5 million newborn deaths per year worldwide, 56% of which occur in "out-of-hospital births", 19% of these are caused by birth asphyxia. In the UK, newborn mortality is much lower but, with the increase in "out-of-hospital" deliveries, it is important that the birth attendant not only be fully conversant with obstetric problems but also be proficient in the techniques of resuscitation in the newborn.

The majority of newborn infants cry within a few minutes of birth and require little more than careful drying and wrapping in a warm towel to prevent heat loss. If the baby does not cry, it should be gently stimulated by more vigorous drying with a towel or flicking the soles of the feet. More vigorous stimulation is contraindicated and can be potentially dangerous.

The newborn baby's initial cry and subsequent efforts at breathing must be assessed carefully to ensure that they result in adequate and sustained oxygenation of the lungs. Gasping without additional efforts at breathing is usually considered inadequate. Abnormal or absent ventilatory patterns require immediate active intervention.

The sequence of resuscitation recommended for

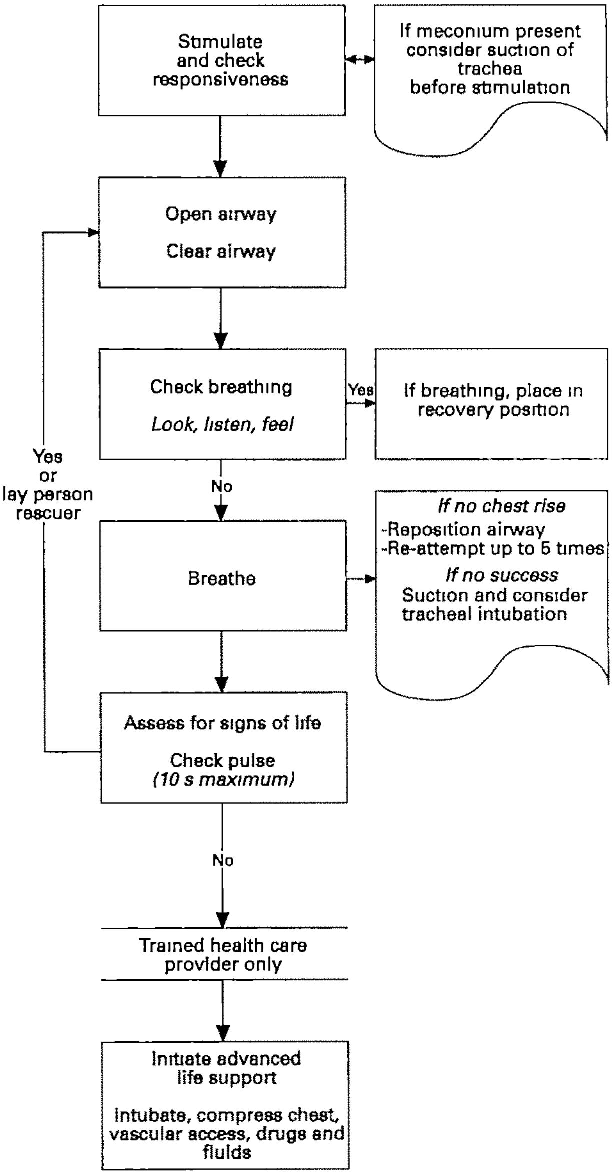
Stimulate and check responsiveness
If meconium present consider suction of trachea before stimulation
Open airway
Clear airway
Check breathing
Look, listen, feel
Yes
If breathing, place in recovery position
Yes or lay person rescuer
No
Breathe
If no chest rise
-Reposition airway
-Re-attempt up to 5 times
If no success
Suction and consider tracheal intubation
Assess for signs of life
Check pulse
(10 s maximum)
No
Trained health care provider only
Initiate advanced life support
Intubate, compress chest, vascular access, drugs and fluids

Figure 3 Algorithm for resuscitation of the newborn.

the newborn follows the same *ABC* sequence as that described for the young infant. The emphasis in the newborn lies with *A* (airway) and *B* (breathing). If *C* (circulation) is needed then more advanced technical interventions, including the use of drugs, are probably required.

AIRWAY

The airway is formally opened by the head tilt, chin lift or jaw thrust manoeuvre. The resuscitator must ensure that the head and neck are not over-extended as this may kink and occlude the soft newborn trachea. Any secretions, mucus or blood should be removed carefully with a suction device but vigorous blind suction of the pharynx must be discouraged as it may induce apnoea and bradycardia.

BREATHING

If clearing the airway does not result in adequate breathing then the birth attendant must commence artificial ventilation as quickly as possible. It is important to recognize that the continued survival of any newborn rests in its ability to take the "first breath" and to continue to breathe. Without the first breath the lungs fail to expand or develop a functional residual capacity. Furthermore, the anatomical changes in the circulation, which in the fetus have enabled blood to bypass the lungs, persist.

In extreme circumstances, when no equipment is available, ventilation can be initiated by mouth-to-mouth and nose ventilation. Because the newborn baby is covered in maternal blood and body fluids associated with birth, this represents a significant health infection risk to the rescuer. Therefore, before commencing this form of expired air ventilation, the face and mouth of the infant should be carefully, but rapidly, cleaned. Ideally, and in most cases, the birth attendant should be equipped with a simple ventilation device, either a bag–valve–mask or an expired air T-tube. A circular mask with a soft seal edge is recommended as it has been found to be more effective, especially in the hands of the inexperienced rescuer. Ventilation rate should be 30–60 bpm and each breath delivered should cause the chest to rise visibly. Excessively high airway pressures must be avoided as they may damage the newborn lungs. Most devices now used for newborn resuscitation are fitted with a pressure limiting valve set at 30–40 cm H_2O. It should be remembered that the first breath may require a slightly higher inspiratory airway pressure to overcome the resistance of the fluid filled airways and the low compliance of the unexpanded lungs.

Continued failure to breathe signals the need for the resuscitator to intubate the trachea with a straight sided tracheal tube of appropriate size using a straight neonatal bladed laryngoscope. Tracheal intubation secures the airway and allows careful controlled ventilation with high concentrations of inspired oxygen. If, on attempting intubation, the trachea is seen to be filled with thick meconium, intubation should continue. Suction is then applied carefully to the tracheal tube as the tube is withdrawn slowly allowing removal of the thick meconium.

CIRCULATION

The newborn heart rate shortly after delivery should be greater than 100 beat min^{-1}. The pulse in the newborn is best assessed by palpating the base of the umbilical cord. Bradycardia should be treated initially by establishing effective ventilation and oxygenation of the lungs but, if there is not rapid recovery of the heart rate, techniques, now considered to be advanced, must be commenced.

Chest compressions in the newborn should be applied only by trained health care providers. If heart rate is less than 60 beat min^{-1} and not improving, chest compressions should be started. Chest compressions can be applied using the same method as for small infants or by applying two thumbs placed side by side over the sternum at the centre of an imaginary line joining the nipples, each hand circulating the child's chest. Compressions are carried out at a rate of 120 events per minute interposing one ventilation between every three chest compressions (a ratio of 3:1 for newborns).

If heart rate fails to respond to chest compressions accompanied by effective ventilation of the lungs with a high concentration of inspired oxygen, the umbilical cord should be cannulated with a 5-French gauge umbilical catheter.

There is still disagreement as to the first pharmacological intervention in advanced neonatal resuscitation.[15] Adrenaline is the favoured choice at a dose of 10 μg kg^{-1} (0.1 ml kg^{-1} of a 1 in 10 000 solution) flushed through the cannula with saline. Some authorities recommend an initial dose of sodium bicarbonate to reverse the acidosis present in the newborn but the dangers of infusing sodium bicarbonate[37 50] and the adverse effects of giving hyperosmolar fluids to neonates[29 93] must be considered carefully. If bicarbonate solution is administered it is given in a dose of 1–2 mmol kg^{-1} (2–4 ml of a 4.2% solution) over 2–3 min. It must be flushed carefully through the umbilical catheter so that it does not inactivate any drug administered subsequently.

Some infants require expansion of their circulating blood volume; 10–20 ml kg^{-1} of cross-matched blood or albumin usually establishes an effective circulation. If there is a history of opioid administration in the mother before delivery, this could be the cause of respiratory depression in the neonate. Naloxone 100 μg kg^{-1} should be given and the infant observed carefully to ensure that respiratory depression does not return when the effect of naloxone wears off. All newborn babies who require intervention beyond that of simple early ventilatory support for a short period of time must be admitted to a special care baby unit for observation, monitoring and continuation of care.

Conclusion

Paediatric life support is an essential part of the resuscitation cycle. To be effective, those practising paediatric resuscitation at basic or advanced levels need to be trained properly and practised in the skills of the procedure. Delay or hesitation in recognizing the need for or performing resuscitation can have disastrous consequences.

The recent publication of International Advisory Statements has simplified the approach to resuscitation by unifying the various national bodies, reviewing the published literature and recommending a single pathway described by the best available medical science. There is still much that is based on unproved theories but with the use of standardized reporting formats it is hoped that these will become fewer and the results of resuscitation will improve.

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Drugs in modern resuscitation

R. VINCENT

Cardiopulmonary resuscitation addresses several life-threatening conditions, broadly classified by presenting cardiac rhythm into ventricular fibrillation (VF) (or pulseless ventricular tachycardia), asystole (with or without P waves) or electromechanical dissociation (EMD). Our greatest therapeutic success follows the correction of the underlying abnormality with minimum delay. Of crucial importance is early electrical defibrillation for patients in VF, airway management and ventilation for those with primary respiratory insufficiency and volume repletion for hypovolaemic EMD.

The role of drugs remains contentious. Animal models have provided data that sometime seem conflicting and are of limited applicability to human cardiopulmonary arrest. Prospective studies during clinical resuscitation are few and have raised doubts more often than provided confirmation of the use of agents that have been used hitherto on theoretical, retrospective or anecdotal evidence.

The use of drugs in modern resuscitation is directed at:

- improving organ perfusion during CPR
- facilitating electrical defibrillation
- preventing the recurrence of malignant ventricular arrhythmias
- increasing excitability and conduction, particularly in nodal tissue during profound bradycardia or asystole
- normalizing important metabolic derangements (including unwanted drug effects) contributing to, or resulting from, the arrest
- protecting the brain (and to a lesser extent the heart) from the effects of prolonged, intense hypoxia.

Physiology of cardiopulmonary arrest and resuscitation

The physiological state of a patient presenting with cardiopulmonary arrest depends on several factors: the precipitating pathology of the arrest, any additional disease processes, prior drug treatment and delay in the initiation of resuscitation. Cardiac arrest after a period of profound hypoxia may be associated with an established metabolic acidosis; prior respiratory obstruction or depression may have generated a respiratory acidosis with elevated P_{CO_2}. Pain in the pre-arrest period triggers a surge in autonomic activity encompassing both adrenergic and cholinergic effects.

Abrupt circulatory standstill, even without a prior biochemical disturbance, has several key metabolic consequences.

HYPOXIA

Cardiac arrest, after a brief period, leads to a steep decrease in arterial P_{O_2}. Moreover, a simultaneously advancing respiratory acidosis shifts the haemoglobin–oxygen dissociation curve adversely, reducing saturation for a given oxygen concentration. Mixed venous blood is severely desaturated as a consequence of arterial hypoxia and a dramatically slow capillary flow in spite of effective CPR.

ACIDOSIS

Acidosis arises from a combination of carbon dioxide retention and steady accumulation of the products of anaerobic metabolism. After the onset of VF, the pH in venous blood samples from the myocardium decreases from baseline to less than 6.8 in approximately 10 min[42]; acidosis in peripheral blood is recordable in a similar time even in the face of immediate CPR.[147] But, it is *tissue* acidosis that develops more rapidly and is the more sinister in its effects.

In the brain, nuclear magnetic resonance spectroscopy during cardiac arrest with external CPR shows a profound decrease in pH within 5–6 min, threatening tissue survival.[21] Tissue acidosis is also seen early in the heart[23] which, as in other cells, follows marked accumulation of carbon dioxide.[94] This change results in reduced myocardial contractility, reduced automaticity of pacemaker cells, a decreased threshold for ventricular fibrillation and opposition to the effects of catecholamines.[104 148] At intracellular concentrations of carbon dioxide greater than 63 kPa,

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Heart, resuscitation. Complications, ventricular fibrillation. Complications, asystole. Acid–base equilibrium. Heart, antiarrhythmics.

RICHARD VINCENT, BSC, MD, FRCP, FESC, AKC, Department of Cardiology, Royal Sussex County Hospital, Brighton and Trafford Centre for Graduate Medical Education and Research, University of Sussex, Falmer.

Address for correspondence: Department of Cardiology, Royal Sussex County Hospital, Eastern Road, Brighton, Sussex BN2 5BE.

resuscitation from mechanical arrest may not be possible.[94]

During CPR, mixed venous blood conveys to the lungs the acidic products of anaerobic metabolism giving rise to a pH of approximately 7.15.[144] It reflects the acid–base status of tissues more accurately than arterial blood which, through effective chest compression and ventilation, may be so cleared of carbon dioxide that its pH lies in the normal or even alkalotic range.[109 144]

CATECHOLAMINES

Cardiovascular collapse is accompanied by a substantial release of catecholamines from the adrenal medulla and adrenergic nerve terminals. Plasma concentrations of adrenaline, noradrenaline and dopamine increase rapidly after acute myocardial infarction[63 90 142] with concentrations that seem proportional to the extent of myocardial damage.[90 91] The highest concentrations of endogenous plasma catecholamines occur after cardiac arrest and CPR where concentrations of up to 50 times baseline have been recorded.[48 67 91 132] Deleterious effects may include hyperglycaemia, hypokalaemia, production of lactate and free fatty acids, and sensitization to arrhythmias. That exogenous catecholamines appear helpful in resuscitation in spite of these changes remains unexplained but suggests an inhibitory effect from the other metabolic derangements of cardiac arrest.[21]

OTHER CHANGES

A variety of other metabolic changes are precipitated by circulatory arrest. These include an increase in adrenal corticosteroids, ADH and blood sugar (with a decrease in insulin and tissue glucose use[97]), in addition to a range of haematological and protein responses that follow a state of shock.[141] An increase in the endogenous metabolite adenosine, which opposes the effects of catecholamines, has also been shown.[135]

HAEMODYNAMIC STATE

Circulatory collapse treated by CPR results in a highly abnormal haemodynamic state. Cardiac output reaches no more than one-third of normal,[27] probably less,[127] and circulation time is substantially slowed. Although perfusion is redistributed to the upper part of the body, particularly the brain and myocardium, animal models show that the calculated minimum required cerebral and myocardial blood flow (18 and 10 ml min^{-1}/100 g tissue, respectively[35 51 99 102 112]) are unlikely to be achieved during CPR without the use of vasopressor agents.[32 84 112]

The driving force, and limiting factor, for myocardial perfusion is aortic diastolic pressure. In animal models a pressure of 30–40 mm Hg is associated with improved survival.[29 103 115 146] At present, this seems best enhanced by pharmacological antagonism to the profound venous and arteriolar dilatation that results from the acidosis of cardiac arrest.[98]

Not surprisingly, the distribution volume and pharmacokinetics of most drugs are altered extensively during cardiac arrest and CPR,[116] and are influenced importantly by the route of administration.

Routes of administration

The routes chosen for drug administration during CPR represent a compromise between the practicality of access and their apparent efficacy to deliver drugs to the central circulation. Peripheral and central veins, and tracheal (endobronchial) administration are the most commonly used routes. The intraosseous route may be worthwhile in children[47] but intracardiac administration has now fallen from favour; other routes (femoral vein, intranasal) seem impractical.

PERIPHERAL VEINS

Drugs injected into the veins of the antecubital fossa during CPR reach a peak in the major systemic arteries at 1.5–3 min after injection.[15 45 82 118] Circulation time is shortened by up to 40%, however, if the bolus drug is flushed into the vein with 20 ml of diluent. This provides an effect similar to that of central venous injection.

The flushing solution now recommended is normal saline to avoid enhancing the metabolic disadvantage of 5% dextrose in worsening the progressive hyperglycaemia of circulatory arrest.[131]

CENTRAL VEINS

Compared with peripheral administration, the delivery of drugs by a central route achieves a faster drug appearance, higher peak concentration and a more potent pharmacological effect.[16 65 82] Kuhn and colleagues, in their classic experiments with indocyanine dye, showed a peak concentration in the femoral artery at 30 s compared with 90 s after peripheral administration[82]; in an animal model, lignocaine reached a concentration of 34.5 mg litre^{-1} after central compared with 22 mg litre^{-1} after peripheral injection[10] and even higher concentrations than this have been recorded in humans. Most workers agree that supra-diaphragmatic central venous administration is the most efficacious route for drug delivery during closed chest compression.[62 140 128]

But in a clinical cardiac arrest other practical issues are relevant. A central cannula requires interruption of CPR and may be hazardous in patients after recent thrombolysis. Even with normal blood clotting, central venous insertion is associated with a complication rate of 1–14%,[41 140] and placement may not be 100% successful.[36 44] Hence a wide-bore antecubital venous cannula through which bolus drugs are flushed with normal saline may best suit drug delivery in practice, at least in the early phase of most resuscitation attempts.[3 4 43]

TRACHEAL

The lung capillary surface area of 70 m^2 offers a potential route for drug administration during CPR, especially as tracheal intubation occurs early in an arrest and may be easier to achieve in practice than i.v. cannulation.[78] One study estimated the time saved by this approach to be 4 min.[133] Adrenaline, atropine, lignocaine, naloxone and bretylium can be given by this route,[56,100,119,134] although absorption may be via the tracheal or bronchial mucosa rather than the alveolar capillary network.

In animals, tracheal administration of adrenaline mimics its effect intravenously[124]; in humans, vasoconstriction traps adrenaline in the lungs to produce a lower plasma concentration and delayed peak[56,131] but a longer duration of action than after i.v. administration.[125] Atropine also has a slower time-course of action by this route.[134]

The dose and dilution of drugs given by the tracheal route remain controversial. Although up to 10 times the i.v. dose may be necessary to achieve the same effect as i.v. administration,[120] current European recommendations[3] are to use twice the usual i.v. dose for tracheal delivery during clinical cardiac arrest. There is conflicting evidence on the optimal diluent in relation to the effects of normal saline and dextrose in both drug absorption and the inevitable transient decrease in therapeutic oxygenation and pH[107] seen after their use.

The efficacy of tracheal delivery is influenced strongly by technique.[93] Currently recommended practice is to inject the drug diluted in 10 ml of normal saline via a catheter that extends to just beyond the end of the tracheal tube, but tracheal administration is now seen as a route to be used only if i.v. access is delayed.

INTRACARDIAC

Intracardiac adrenaline has been proposed since the turn of the century,[29] and drug delivery by this route has often focused on other pressor agents.[64] But the technique of injection into the right ventricle by the sub-xiphoid route requires considerable expertise and may not be successful, often delivering the drug to an extra-cardiac site. Transection of the left anterior descending coronary artery can occur with a precordial, left parasternal route. Intracardiac delivery is now seen as a last resort.

Catecholamines and other vasopressors

Adrenaline is undoubtedly effective in improving the haemodynamic state of the patient during resuscitation. Cerebral and myocardial blood flow is enhanced by preventing arterial collapse and by augmenting aortic diastolic pressure by an increase in peripheral resistance.[29,76,98,111,115,146] These effects are mediated primarily through stimulation of alpha$_1$ and alpha$_2$ receptors. Alpha$_1$ receptors are found near the outer wall of peripheral vessels, respond primarily to neuronally released noradrenaline[18] and may be down-regulated or desensitized by the metabolic milieu of a cardiac arrest. Alpha$_2$ receptors are located near the vascular lumen, respond primarily to circulating catecholamines and may play a more an important role in regulating vasomotor tone during resuscitation.[21]

The contribution of the additional effect of adrenaline at beta$_1$ and beta$_2$ receptors is unclear. Beta$_1$ effects appear to have no advantage in restoring a spontaneous circulation from VF, asystole or EMD; moreover, adrenaline at high doses may increase myocardial oxygen consumption and may predispose to later arrhythmias.[17,31,74] Although it is difficult to show benefit from beta$_2$ stimulation in restoring spontaneous circulation,[87] this action has been shown to dilate the cerebral microvasculature[40] and improve cerebral perfusion.[20]

The optimum dose of adrenaline has been a matter of continuing interest and debate fuelled by conflicting evidence.[16,19,20,52,61,78,92] Animal studies have indicated repeatedly the benefit of doses of adrenaline 3–10 times higher in a weight-adjusted bolus than is currently used in humans (approximately 15 mg kg^{-1}). A dose-dependent improvement in regional myocardial and cerebral blood flow has been recorded during closed chest compression in animals over the range 0.02–2.0 mg kg^{-1}[16,19,20,61] and similar data have now been found during human cardiac arrest.[52,113] More recent prospective, controlled clinical studies in adults[17,22,138] showed an improvement in the return of spontaneous circulation with higher doses, but no improvement in survival to hospital discharge. One study[88] showed preferential benefit in patients with EMD or asystole when treated with 5 mg rather than 1 mg of adrenaline but, perhaps because of a type II error, the result did not reach clinical significance.

Vasopressor agents other than adrenaline seem theoretically attractive in providing powerful alpha adrenergic stimulation while avoiding potentially deleterious beta effects. There are few reports on the comparative benefit of noradrenaline, although its action on alpha$_1$ and alpha$_2$ receptors allows it to mimic adrenaline in its ability to improve myocardial and cerebral blood flow. In one study by Lindner, Ahnfeld and Grunert,[87] the effect of 1 mg doses of noradrenaline and adrenaline were compared; noradrenaline resulted in a greater than two-fold increase in the return of spontaneous circulation but had no effect on survival to hospital discharge.

In contrast, methoxamine and phenylephrine (predominantly alpha stimulants) are less effective in promoting coronary and cerebral blood flow[16,19,20] even at doses that result in an equivalent increase in aortic diastolic pressure and a rate of return of spontaneous cardiac output. This phenomenon has been attributed to the lack of effect of these agents on alpha$_2$ receptors[21] or to the "missing" effect of beta$_2$ stimulation which may contribute to a successful outcome.

The nearly pure beta agonist, isoprenaline, has a predictably adverse effect on the circulation during cardiac arrest. Beta$_2$-mediated vasodilatation causes a decrease in mean arterial pressure reducing coronary perfusion while its beta$_1$ effects threaten an increase in myocardial oxygen requirements. The sole indication for isoprenaline is that of short-term chronotropic support of a patient en route to electrical pacing for haemodynamically significant bradycardia.[4,43] A brittle response may be seen even with careful titration of the i.v. infusion, and hypokalaemia and ventricular arrhythmias may be induced.

There is no mandate from the data currently available to suggest a policy for catecholamine administration during cardiac arrest other than that embodied in the European and American guidelines.[3,13]

Atropine

Atropine blocks cholinergic muscarinic receptors and isolates the heart from the effect of the parasympathetic nervous system, particularly in nodal tissue. As a result, the automaticity and conduction of both sinoatrial and atrioventricular nodes are enhanced.

Atropine is most effective when a haemodynamically significant bradycardia results from high vagal tone (pain, vomiting, facial cold or trauma), global hypoxia or sensitization of nodal tissue to the effect of the vagus as a result of ischaemia. Its effect in asystole or EMD caused by widespread myocardial damage is negligible. In a few settings, a small number of asystolic patients have shown short-term benefit, but no survivors have been recorded attributed solely to the use of atropine.

Used as an agent for peri-arrest bradycardias, the dose is best balanced against its effect,[2] bearing in mind that (i) 0.5 mg may exert an agonist action with a resulting bradycardia and susceptibility to VF,[30] and (ii) 3 mg produce a fully vagolytic effect.[110] The adverse effects of atropine (delirium, tachycardia, coma, hot skin, ataxia, urinary retention, blurred vision and pupillary muscle dilation), however, are usually regarded as benign.

Antiarrhythmic agents

Electrical defibrillation remains the key treatment in most cases of successful adult resuscitation, but in this setting antiarrhythmic drugs have three potential uses:

- to terminate a malignant ventricular arrhythmia
- to facilitate electrical defibrillation
- to prevent the recurrence of VT or VF.

Antiarrhythmic drugs are commonly classified according to their cellular mechanism of action—the Vaughan–Williams classification (table 1). Few have properties limited solely to a single cellular effect and some (particularly bretylium and amiodarone) have clear actions in two or three classes.

Table 1 The Vaughan–Williams classification of antiarrhythmic drugs

Class of action	Examples
Class I: Blockade of sodium channels:	
A Moderate prolongation of conduction and repolarization:	Quinidine Procainamide Disopyramide
B. Minimal effect on conduction and repolarization:	Lignocaine Mexiletine
C. Marked prolongation of conduction:	Flecainide Propafenone
Class II: Blockade of β adrenergic receptors.	Propranolol Atenolol
Class III: Prolongation of repolarization:	Amiodarone Bretylium Sotalol
Class IV: Blockade of calcium channels:	Verapamil Diltiazem

Agents of classes I, II and III are effective in the prevention of ventricular arrhythmias, but their use in practice is often limited by their unwanted actions: myocardial depression, proarrhythmic action and non-cardiac side effects. Moreover, their ability to suppress benign arrhythmias while exerting little influence on the incidence of unheralded VF or mortality have also diminished enthusiasm for their use. The agents in centre stage of modern resuscitation are lignocaine, bretylium and amiodarone, with supporting appearances by other class I and class III agents.

LIGNOCAINE

Lignocaine is a class IB agent which depresses excitability by blocking sodium channels without extending action potential duration. In animal models it also has an antifibrillatory action, although this requires higher doses than those necessary to suppress ventricular ectopic beats.[5,25,145]

Lignocaine suppresses impulse formation in the sinus node.[89] It has little effect on AV nodal conduction but may impede conduction below the bundle of His. Conveniently, lignocaine produces only weak myocardial depression,[28] has little effect on vasomotor tone and does not reduce coronary perfusion pressure during resuscitation. Its proarrhythmic action is also weak and although its CNS side effects include restlessness and convulsion, these are seen rarely.

Lignocaine is of undoubted value in the treatment of ventricular extrasystoles and tachycardia, particularly in acute myocardial infarction. Its ability to prevent ventricular fibrillation in this context has also been demonstrated in several small studies[95,58] and in a larger prospective study by Koster and Dunning[80]; however, there is no convincing proof of an improvement in overall mortality as a result.[59] Two explanations have been offered: a higher occurrence of subsequent asystole that results from the use of this drug[142] and failure to use experimental conditions that would best show benefit in this regard.[24]

The contribution of lignocaine during an arrest to aid resuscitation from refractory VF remains contentious. Animal models have shown that it causes a marked increase in defibrillation threshold (increasing the energy required for cardioversion),[9,33,38,66] but data from limited human experiments are sparse.[24] Small-scale studies taken together have produced equivocal results.[57,106] Where success has occurred, lignocaine may have acted by preventing the immediate recurrence of VF rather than by facilitating the effect of the DC shock.[24,106]

Whether lignocaine results in an improved outcome from cardiac arrest in sustained VF was explored recently[58] in a retrospective observational study over a 12-yr period of 1212 cases treated outside hospital in Goteberg. This resulted in a comparison of 185 patients who had received lignocaine with 105 who had not. In the lignocaine group, 45% showed a return of spontaneous circulation compared with 25% in the group who had not received lignocaine ($P<0.001$). Comparable values for survival to reach hospital (38% *vs* 18%) were also significantly different ($P<0.05$). However, there was no difference in the rate of hospital discharge between the two groups (14% *vs* 8%; ns). Although treatment with lignocaine appeared to be an independent predictor for the return of spontaneous circulation and hospital admission, patients in the lignocaine group also received adrenaline and were attended by a nurse, both of which were rare in the non-lignocaine group. The results of controlled prospective studies of lignocaine and alternative antifibrillatory drugs are still needed.

BRETYLIUM

Introduced initially as an antihypertensive agent with adrenergic neurone blocking properties, bretylium was shown first to have important antifibrillatory actions in 1965.[85] As a class III agent it increases myocardial stability, elevating the threshold for VF and rendering more uniform the action potential duration between ischaemic and non-ischaemic tissue.[5 25]

Bretylium may lower the threshold for defibrillation[26 34] and should therefore aid recovery from VF. Not all investigations have reported this effect, however,[66 77] and little difference has been found between bretylium and lignocaine in small clinical studies.[77 106] The theoretical benefit of bretylium on defibrillation threshold may be outweighed by a subsequent action in producing EMD and post-arrest hypotension.[46] Bretylium appeared better than placebo during pre-hospital arrest[105] but the data were retrospective and uncontrolled. Prospective studies for this agent are mandatory.

AMIODARONE

First launched as a coronary vasodilator, the anti-arrhythmic properties of amiodarone were characterized first in 1970.[70 136] Its broad spectrum of activity and its favourable effect on myocardial contraction make it an attractive agent. In common with bretylium, amiodarone is a potassium channel blocker which lowers the defibrillation threshold. It also has a powerful antifibrillatory action.[114] Its effect in lengthening action potential duration places it in class III of the Vaughan–Williams classification but it also inhibits sodium-dependent depolarization giving it additional class I activity. Furthermore, it exhibits a degree of non-competitive beta blockade.[117]

Amiodarone has a weak depressant effect on the SA node and on AV nodal conduction. Its mild, and usually transient, negative inotropic effect appears restricted to rapid i.v. administration. Its peripheral vasodilatation, however, could theoretically oppose the beneficial action of pressor agents in supporting the circulation of the collapsed patient.

The efficacy of amiodarone for the treatment of malignant ventricular arrhythmia is well documented,[81 101] and its beneficial effects for secondary prevention in patients with acute myocardial infarction, congestive failure and primary ventricular arrhythmias have been explored extensively, generally with encouraging results. But the value of amiodarone during cardiac arrest has received little attention[149] and its inclusion in the resuscitation armamentarium is confined to the area of peri-arrest arrhythmias.[2]

Alkalizing agents

At the time when procedures for resuscitation became routine clinical practice, i.v. administration of sodium bicarbonate seemed a logical step to counteract the tissue acidosis found in cardiac arrest. In the mid 1980s this view was challenged. The hypothesis introduced by Weil and colleagues[54 144] was that carbon dioxide elimination was limited more by poor tissue perfusion than alveolar hypoventilation; also, the extensive production of carbon dioxide that follows i.v. administration of sodium bicarbonate would re-accumulate in the tissues themselves further reducing intracellular pH and adversely affecting outcome. Several key points of this argument have been challenged recently.[21]

First, although inadequate perfusion in an arrest limits carbon dioxide elimination, correctly performed CPR, supported by the vasopressor effect of adrenaline, remains effective and is one of the mainstays of the control of acid–base balance during resuscitation.

Second, i.v. administration of bicarbonate may not persistently increase venous carbon dioxide during CPR. Doubt about the validity of the results of previous experiments, both in humans[1 144] and animals,[50 69] have been voiced by Brown and colleagues[21] on the basis of experimental design; it is also possible that this phenomenon, if real, is transitory over a matter of only a few minutes.

Third, a major argument against the use of bicarbonate during CPR is that it worsens intracellular acidosis.[70] The pivotal study on which this theory rests is that of Bernyi, Wolk and Killip[11] whose experimental dogs received bicarbonate 10 mmol kg^{-1} over a 20-min period of resuscitation. As this represents a dose of 700 mmol in humans, the clinical relevance of this experiment must be open to doubt. Additional evidence has been published that both supports[71 137] and refutes[69 126 130] the adverse effect of sodium bicarbonate on cytoplasmic pH, particularly in myocardial cells.[86]

Finally, what evidence is there that bicarbonate alters the clinical progress of resuscitation? Both positive[72 123 129] and negative[50 55 68 130] results have been reported from experiments in animals. But no prospective controlled studies have been performed to demonstrate the effect of sodium bicarbonate on the outcome of cardiac arrest in humans. Retrospective studies suffer from the association of bicarbonate administration with arrests that were inevitably prolonged and therefore unlikely to be successful.

For brief resuscitation procedures, sodium bicarbonate is probably irrelevant having neither a good nor a bad effect,[12 14 55] but its use in prolonged (>10 min) arrests needs careful evaluation. Administration of a buffer to correct lactic acidosis in a hypoxic state has been shown to decrease cardiac output by reducing left ventricular contractility, a

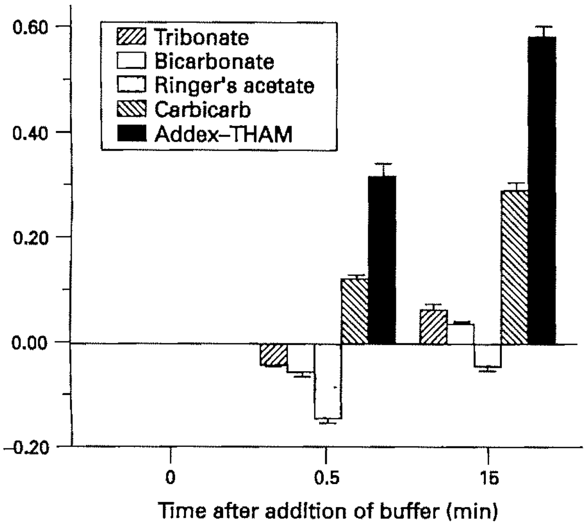

Figure 1 Changes in cytoplasmic pH (pH_i) after addition of Tribonate, sodium bicarbonate, Ringer's acetate, Carbicarb or Addex-THAM (mean, SEM) to suspended rat myocardial cells during hypoxic conditions (from Li, Wiklund and Bjerneroth,[86] with permission).

change associated with an increase in lactic acid production and a reduction in blood pH.[7,53] A large prospective human study of buffer therapy in cardiac arrest[37] also failed to show benefit. But advantages have been reported in relation to the reduction in defibrillation threshold,[72] higher rates of return of spontaneous circulation,[123] reduced incidence of recurrent VF,[72] improved neurological outcome[83,123] and increased rates of hospital discharge.[39] Benefit appears to follow a titrated dose of bicarbonate to replenish the depleted HCO_3 ion and the concurrent use of adrenaline,[13] the effect of which is enhanced by pH correction.[96] (In the absence of adrenaline, hypertonic buffers limit coronary perfusion pressure.) Buffer agents other than bicarbonate have been explored chiefly in animal models. In an experiment by Li, Wiklund and Bjerneroth,[86] bicarbonate, Tris buffer (trometamol), Tris buffer mixture (Tribonate), Ringer's lactate and Carbicarb were tested in a cellular model of hypoxic cardiac arrest. Figure 1 shows the resulting change in pH from the initial acidotic cytoplasmic pH of 6.85. The most favourable agent was judged to be Tribonate which, in larger doses, caused almost complete correction of intracellular acidosis without overcompensation. No clinical benefit, however, has yet emerged from the use of this agent.[37]

At this stage, to abandon bicarbonate therapy completely seems unwise but its use appears best confined to the later stages of cardiac arrest where effective ventilation and chest compression have been established for some while, where adrenaline has been used to support vascular collapse according to existing procedures and where the dose can be titrated in a manner that allows balanced repletion of the bicarbonate ion.

Calcium and magnesium

CALCIUM

Although ionic calcium is intimately involved in impulse formation and excitation–contraction coupling, human studies have shown that its contribution as a pharmacological agent to recovery from any form of cardiac arrest is negligible or adverse.[139]

The accumulation of intracellular calcium that results form profound ischaemia promotes myocardial damage and impaired neurological outcome. Exogenous calcium may amplify these effects[49,150] and is therefore indicated only if the patient presents in the unusual state of drug overdose with calcium channel blocking agents.[3,43]

MAGNESIUM

Magnesium mirrors the action of increased extracellular potassium in stabilizing the myocardial cell membrane.[8] In contrast, decreased intracellular magnesium (often resulting from the diuretic treatment that depletes potassium) renders the myocardium more excitable and thus more prone to ventricular arrhythmias.[60,122]

Exogenous magnesium has been shown to suppress ventricular extrasystoles not only in a depleted state but also when plasma and tissue concentrations are normal.[121] An additional "pharmacological" action is therefore postulated. The place of magnesium in cardiac arrest is uncertain[6] and untested but the use of 10 ml of a 50% solution of magnesium sulphate is unlikely to be harmful when the patient is known to have prior hypokalaemia.

Conclusion and future directions

Patients most likely to recover from cardiac arrest are those who collapse because of VF and who receive successful electrical defibrillation within 90 s. The chances of survival are poor if three shocks in rapid succession, together with basic life support, fail to restore a spontaneous output; any pharmacotherapy at this stage represents a last "desperate effort to resuscitate".[108]

"Most drug regimens in resuscitation, even those in use for many years, are based on animal evidence, indirect evidence and common sense. They are rarely based on sound clinical experiments because of practical and legal constraints. No drug used in resuscitation has benefit established unequivocally according to the principles of 'evidence-based medicine'. Moreover, no drug whether it be epinephrine, lidocaine, or bicarbonate, which are the most widely used can be given without risks; the possibility of adverse outcome because of overdose is a real possibility, but equally difficult to prove."[79]

This slightly pessimistic quote should not detract from the attempts that have been made (with increasing scientific rigour) to set the understanding and treatment of cardiac arrest on a secure scientific base. Prospective clinical studies of most of the "accepted" agents are warranted in addition to the development of more tailored drugs that could reverse the rapidly degenerating metabolic milieu of circulatory standstill. Agents to enhance tissue perfusion during CPR, to retard hypoxic cellular necrosis buying time before definitive treatment can be given and to facilitate electrical defibrillation are the highest priorities for research.[21]

But the difficulties of research in human resuscitation are substantial. Operational, ethical and scientific hurdles are the most challenging of all in this setting. Yet such research is mandatory to secure the most effective regimens for resuscitating collapsed patients; these hurdles should not be allowed to prevent the inclusion of sufficient numbers of patients to obtain statistically and clinically significant results. Meanwhile, adherence to the consensus recommendations of the major bodies with an interest in resuscitation, particularly with regard to the agents discussed, is advised.[3 43 75]

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Peri-arrest arrhythmias

D. CHAMBERLAIN

Many victims of cardiac arrest suffer the event in the context of a critical illness complicated by malignant rhythm disorders. Moreover, almost all patients who are resuscitated initially from a cardiac arrest have a subsequent course characterized by bradyarrhythmias or tachyarrhythmias which are likely to need treatment to restore an adequate circulatory state or to prevent further collapse. Thus competence in the management of cardiac arrest *per se* is an incomplete skill for those—usually not cardiologists—who aspire to practice advanced cardiac life support. They should also be able to recognize and treat cardiac arrhythmias that are of their nature potentially malignant or that may become life threatening in some clinical contexts—notably in the aftermath of cardiac arrest. The term "peri-arrest arrhythmias" encompasses all rhythm disorders in these situations. Guidelines on the management of peri-arrest arrhythmias published by the European Resuscitation Council[1] and subsequently revised[2] offer advice at three levels: treatment modalities that might reasonably be expected from any individual treating a cardiac arrest; when expert help should ideally be sought; and advanced management strategies that might be considered when expert help is not immediately available.

Peri-arrest arrhythmias that may lead to or complicate cardiac arrest are considered under three broad headings: bradycardias and two types of tachycardias. The designation of bradycardia usually relates to disorders of heart rhythm with a rate of less than 60 beat min^{-1}. But this can usefully be extended beyond the conventional definition to include the concept of "relative bradycardia", applicable to heart rates that are greater than 60 beat min^{-1} yet inappropriately slow within the clinical context. A heart rate, for example, of 70 beat min^{-1} may be the modal value in healthy adults yet abnormally slow to a degree that calls for treatment in the presence of cardiogenic shock. Tachyarrhythmias are conventionally divided into those that arise within the ventricle (ventricular tachycardia) or above (supraventricular tachycardia). This classification has merit based on principles of pathological substrate, aetiology, treatment, prognosis and usage, but is presented in the guidelines in a modified form to take account of diagnostic difficulties.[10] Ventricular tachycardia characteristically has a broad QRS complex reflecting delayed depolarization through abnormal pathways, but a minority of tachycardias arising below the AV node may show complexes with a width that lies within the normal range. Supraventricular tachycardia, on the other hand, characteristically shows a narrow QRS complex that is often very similar in shape to that of the usual beats, but two common exceptions cause confusion. First, normal conduction is not possible at very high rates, in particular the right bundle may fail under these conditions so that the pattern of depolarization may be abnormal with a wide QRS of a right bundle branch block pattern even in rhythm disorders arising in the atrium or within the AV node. This so-called rate-related aberration is more common in the presence of heart disease. Second, a pattern of depolarization that is abnormally prolonged during an individual's normal rhythm is at least as prolonged during tachycardia. Thus the width of the QRS complex during tachycardia does not reliably distinguish ventricular from supraventricular origin. Many other features may indicate the true origin of a tachycardia, but accurate classification may be difficult and may not always be possible from the surface electrocardiogram. The guidelines therefore make no assumption that the origin of a tachycardia has been defined accurately. Recommendations for treatment are based instead on the simple classification of narrow complex tachycardias (which are usually supraventricular and may be treated as such with acceptable safety) and broad complex tachycardias (which should be assumed to be ventricular for purposes of treatment as this is the safer strategy).

Separate algorithms are available for bradycardia, narrow complex tachycardia and broad complex tachycardia. The principles of treatment are similar to those used in any clinical context, but the following points should be noted:

- The algorithms are designated specifically for the peri-arrest situation but they cannot encompass all situations that may arise.
- The algorithms are intended for physicians (or those working under the direction of a physician)

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Key words
Heart, arrhythmia. Complications, arrhythmia. Complications, cardiac arrest.

DOUGLAS CHAMBERLAIN, CBE, MD, DSC (HON), FRCP, FRCA, FESC, FACC, Royal Sussex County Hospital, Eastern Road, Brighton BN2 5BE.

who do not regard themselves as experts in arrhythmia management. Therefore, management strategies that are complex or potentially dangerous when used inappropriately are omitted as far as possible.

- The algorithms have to be broadly applicable in all European countries notwithstanding different traditions of antiarrhythmic therapy. Some drugs have been omitted as options because they are not universally available, and alternatives have been offered where it is necessary to do so.
- The algorithms assume that oxygen is being administered and i.v. access is available.
- The arrows indicating progression from one treatment to the next are to be followed only if the arrhythmia is still present.
- All antiarrhythmic strategies (physical manoeuvres,[22] drugs[13] or electrical treatment[7]) can be proarrhythmic. Deterioration may therefore occur as a result of treatment rather than as a consequence of lack of effect. Moreover, the use of multiple antiarrhythmic drugs or high doses of a single drug can cause myocardial depression and hypotension. How far sequential treatments should be pressed in the face of these risks may be a matter for careful clinical judgment.
- The algorithms provide doses based on average body weight and may need adjustment, particularly for small individuals. Doses expressed in mg/kg body weight are judged inappropriate for use in emergency situations because calculations are more likely than usual to introduce error.

Bradycardia

The algorithm for bradycardia is shown in figure 1. The apparent complexity is misleading because the management principles are simple and may be summarized thus: if there is a risk of asystole, pace as soon as possible; *if there is no perceived risk of asystole but the haemodynamic state of the patient is poor, give atropine and pace only if this is ineffective; if there is no perceived risk of asystole and the patient is not compromised haemodynamically to an important degree then only observation is required.* The algorithm, however, provides more information around this framework.

The first and most important decision relates to whether or not there is a perceived risk of asystole. Observed performance of the heart rhythm provides a guide. A history of asystole is a self-evident risk factor in this regard. A pause longer than 3 s also causes concern because reliable subsidiary pacemakers should provide escape beats within a briefer interval. Other criteria in the presence of heart block are based on indications that the site of block is either in the region of the AV node itself (in which case reliable and adequate subsidiary pacemaker tissue should still be available to drive the ventricle) or alternatively below the AV node (in which case any subsidiary pacemakers may be irregular, are likely to be unduly slow and are certainly unreliable). Thus complete heart block with a narrow QRS complex is not in itself an indication for treatment. Conversely, an abnormally wide QRS complex with complete atrioventricular block implies that the subsidiary pacemaker cannot conduct through the usual pathways and may therefore be below the division of the bundle of His into its bundle branches (unless there is pre-existing bundle branch block or the rare phenomenon of bradycardia-dependent bundle branch block). Mobitz type II AV block which is the last of the criteria requires more explanation. During the evolution of AV block a phase usually occurs when some beats are conducted and some are not. This is known as second degree block but there are two types: for a "benign" block in the region of the AV node, intermittent failure of conduction is characterized by dropped beats in Wenckebach periods (also known as Mobitz I block); alternatively, when the failure is within the bundle branch system, the dropped beats occur unpredictably: there is no "warning" PR prolongation. Another marker of problems within the bundle branch system is also present and very obvious. Intermittent failure of a depolarization wave to conduct through the bundle branch system occurs only if one of the bundle branches has previously failed, so that even the conducted beats show bundle branch block of some type. Mobitz type II second degree AV block is therefore characterized by wide QRS complexes in the conducted beats, together with intermittent abrupt failure of conduction. The risk is clear: one bundle branch has already failed and the other is indicating it may do so with no reliable pacemaker tissue available at a lower level.

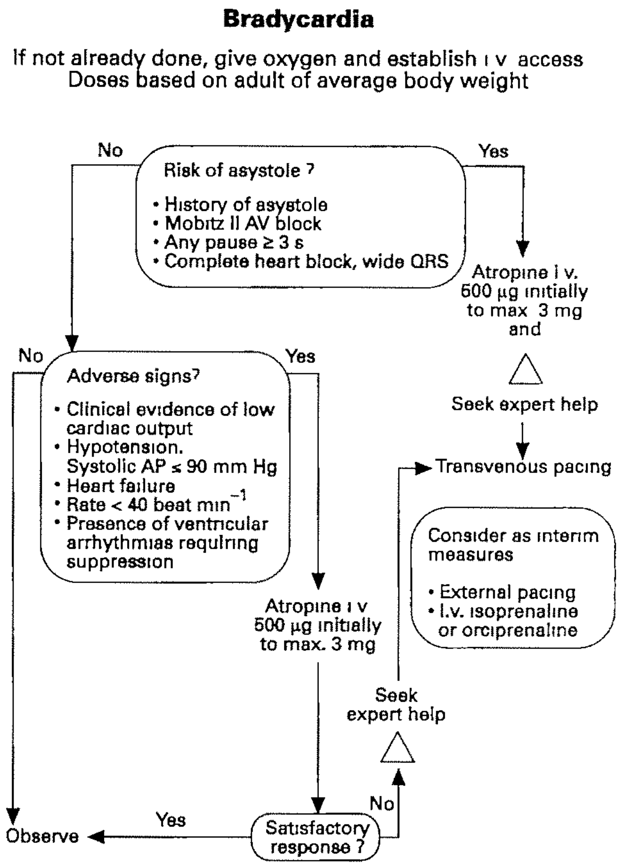

Figure 1 Algorithm for bradycardia

If any of the warning signs are present indicating that asystole is a definite risk, transvenous pacing should be established as soon as possible. The responder who is not an expert in arrhythmia management may wish to do no more than establish i.v. access and give atropine in a dose of 500 μg to 3 mg while waiting for expert help from others with the necessary specific skills. In this situation, however, the use of atropine is frequently unsuccessful. When a patients's condition is critical, external pacing[8] with appropriate sedation should be considered: it is simple to implement provided the equipment is available. The judicious use of isoprenaline is an alternative strategy, with the usual starting dose of 1 μg min^{-1} which may be increased 10-fold or more in a desperate situation, always having regard to the risk of precipitating or worsening ventricular arrhythmias and increasing myocardial oxygen consumption. Orciprenaline is an alternative chronotropic catecholamine used in some countries.

The second decision for those not at immediate risk of asystole is based on the presence or absence of adverse haemodynamic signs. Clinical evidence of low cardiac output, hypotension (arterial pressure less than 90 mm Hg) and overt heart failure are self-evident factors. Heart rate less than 40 beat min^{-1} is included because complications are likely to occur even if such a slow rhythm is tolerated temporarily. The last of the criteria relate to prognostically or haemodynamically important ventricular arrhythmias—either complex forms of ventricular extrasystoles or non-sustained runs of ventricular tachycardia—which occur frequently with or as a complication of an underlying bradycardia. These are best treated by increasing the underlying rate. If an antiarrhythmic is used in this setting, bradycardia is likely to become worse and thus increase the risk from ventricular arrhythmia. In the presence of any of the five adverse haemodynamic signs, atropine should be administered, starting with an initial i.v. dose of 500 μg repeated to a maximum of 3 mg which provides virtually complete vagal blockade.[6] This usually produces a satisfactory response at least temporarily, but if necessary expert help would be needed with a view to transvenous pacing. Only rarely does a patient's haemodynamic condition justify the use of external pacing or the risky chronotropic catecholamines while awaiting definitive treatment.

Bradycardias that do not carry a risk of asystole and are not likely to have important adverse haemodynamic effects require no treatment. Indeed, in the context of myocardial infarction they may have a favourable influence by limiting myocardial oxygen requirement

Broad complex tachycardia

The algorithm for broad complex tachycardia is shown in figure 2 and can be summarized into three possible treatment policies: *if there is no pulse as a result of the arrhythmia the condition should be treated as cardiac arrest using the ventricular fibrillation/ventricular tachycardia algorithm for cardiac arrest; if there is a pulse but inadequate perfusion, cardioversion is required as soon as possible. If there is a broad complex tachycardia without adverse haemodynamic disturbance, routine antiarrhythmic therapy should be used, with cardioversion only if this fails.* The algorithm provides further information around this framework.

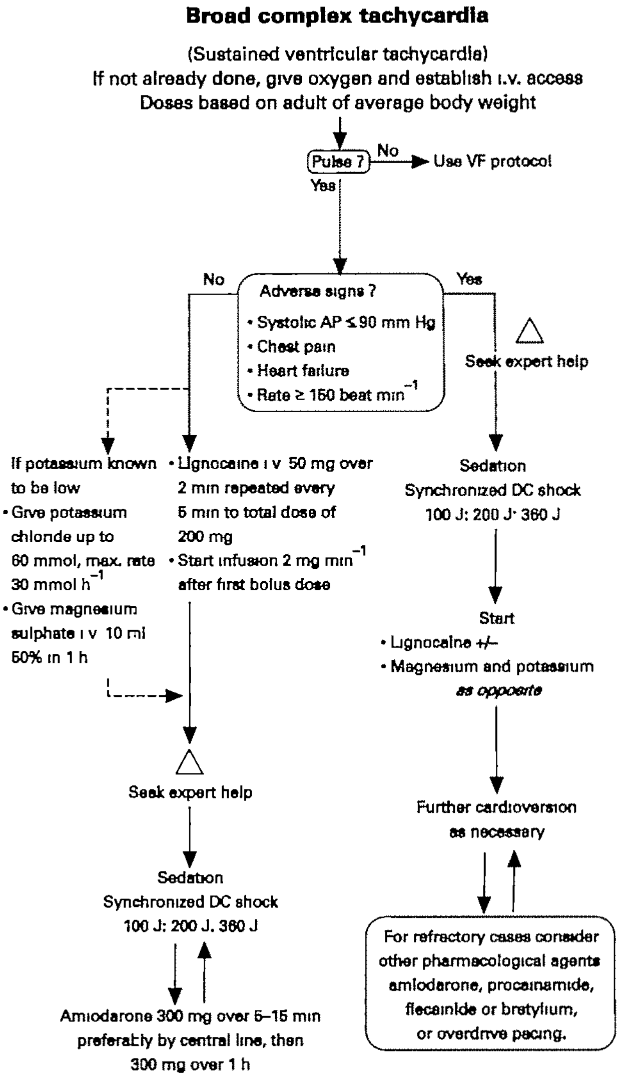
Broad complex tachycardia
(Sustained ventricular tachycardia)
If not already done, give oxygen and establish i.v. access
Doses based on adult of average body weight
Pulse ?
No
Use VF protocol
Yes
No
Adverse signs ?
• Systolic AP ≤ 90 mm Hg
• Chest pain
• Heart failure
• Rate ≥ 150 beat min⁻¹
Yes
Seek expert help
If potassium known to be low
• Give potassium chloride up to 60 mmol, max. rate 30 mmol h⁻¹
• Give magnesium sulphate i v 10 ml 50% in 1 h
• Lignocaine i v 50 mg over 2 min repeated every 5 min to total dose of 200 mg
• Start infusion 2 mg min⁻¹ after first bolus dose
Sedation
Synchronized DC shock
100 J: 200 J: 360 J
Start
• Lignocaine +/-
• Magnesium and potassium as opposite
Seek expert help
Further cardioversion as necessary
Sedation
Synchronized DC shock
100 J: 200 J. 360 J
Amiodarone 300 mg over 5–15 min preferably by central line, then 300 mg over 1 h
For refractory cases consider other pharmacological agents amiodarone, procainamide, flecainide or bretylium, or overdrive pacing.

Figure 2 Algorithm for broad complex tachycardia.

The first decision relates to the presence or absence of a palpable pulse, with the implication that a victim with an absent pulse is also unconscious and clinically in cardiac arrest. When this is not the case, a second decision is reached, relating to adverse signs. These include hypotension (arterial pressure less than 90 mm Hg) and heart failure as for bradycardia, but also the presence of chest pain which might either be the result or the cause of the rhythm disorder, and any rate faster than 150 beat min^{-1} because this is likely to presage problems even if it does not do so at the onset. If any of these signs are present the situation must be regarded as an emergency and expert help should be sought even before sedation and synchronized shock are considered. Energies less than 100 J should not be used because they may have proarrhythmic effects, so attempts at restoration of a more satisfactory rhythm should use sequentially 100 J, 200 J and 360 J. In the unlikely event of cardioversion being unsuccessful, the algorithm recommends the use of lignocaine

50 mg over 2 min, repeated every 5 min to a total dose of 200 mg with an infusion of 2 mg min^{-1} set up after the first bolus dose. If the concentration of potassium is known to be less than 3.6 mmol litre^{-1}, especially in the presence of recent infarction,[15] potassium chloride should be given in a dose of up to 60 mmol, but the maximum infusion rate should never exceed 30 mmol h^{-1}. Magnesium concentrations should be assumed to be deficient in the presence of hypokalaemia, and this is corrected by magnesium sulphate i.v.[24] in a dose of 10 ml of a 50% solution over 1 h. If the arrhythmia persists, further shocks should be attempted when lignocaine 200 mg has been administered: in the presence of adverse signs it is inappropriate to delay electrical treatment for full correction of electrolyte deficiencies. Other drugs that may be used if cardioversion is not successful after lignocaine include amiodarone,[16] procainamide,[14] flecainide,[20] propafenone[17] or bretylium[3]: any one of these may sometimes reverse the arrhythmia or act as successful adjuncts to cardioversion. Clearly every drug that is administered unsuccessfully adds to myocardial depression, and polypharmacy can be justified only in desperate situations. Overdrive pacing[25] is a method of controlling ventricular tachycardia without a persistent adverse effect on heart function, but it calls for considerable expertise in arrhythmia management.

For broad complex tachycardia that is not causing appreciable adverse signs, the lignocaine regimen should be started before any attempts at cardioversion, and hypokalaemia is treated concurrently. If this is not successful expert help should be sought. The management is then likely to consist of synchronized shock (100 J, 200 J, 360 J), with amiodarone as the recommended adjunctive therapy if shock alone is unsuccessful or if the arrhythmia is recurrent.[21] The time for completion of the amiodarone infusion is more than 1 h, but assessment of urgency on clinical grounds will determine how long should elapse before further shocks are given after the first set of three have been unsuccessful.

Narrow complex tachycardia

This is almost always supraventricular tachycardia, and as a peri-arrest arrhythmia is less frequent and somewhat less hazardous. Supraventricular tachycardias are, however, a recognized trigger for malignant ventricular arrhythmias in some clinical contexts,[12] including myocardial ischaemia, and atrial fibrillation is a relatively common peri-arrest arrhythmia.

The algorithm shown in figure 3 can be summarized as follows: *for regular supraventricular tachycardias, vagal manoeuvres or adenosine may be tried first, but if these are not successful in the presence of adverse signs the first strategy is cardioversion; without adverse signs there is a choice of routine antiarrhythmic agents that include a short-acting beta-blocker, digoxin, verapamil and amiodarone.* The algorithm adds further details to this outline.

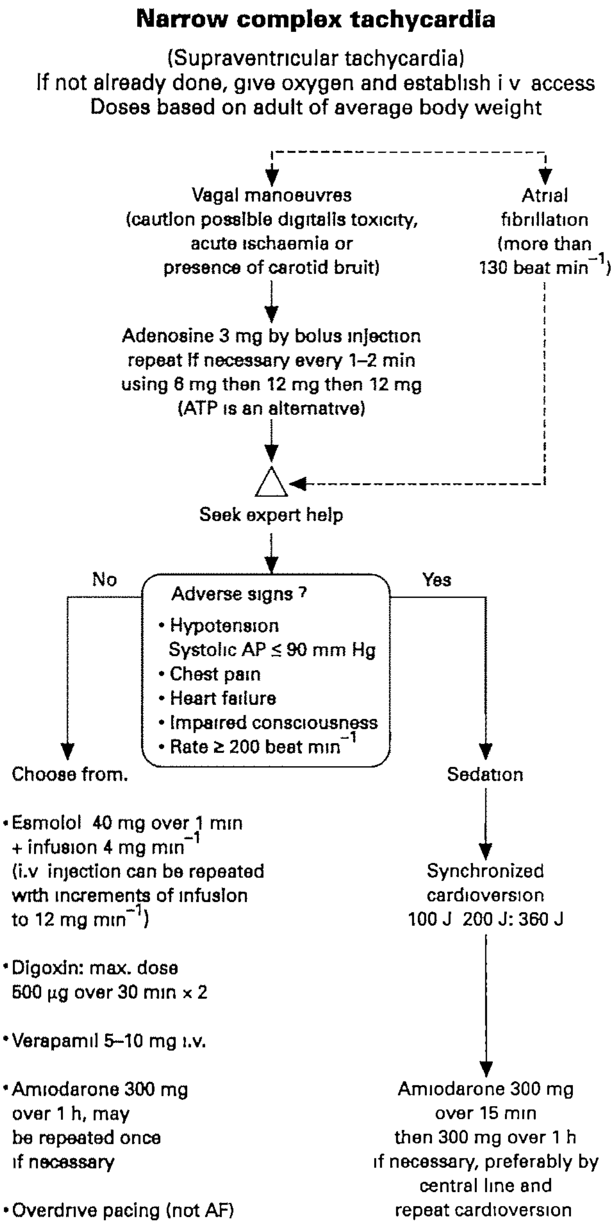
Narrow complex tachycardia
(Supraventricular tachycardia)
If not already done, give oxygen and establish i v access
Doses based on adult of average body weight
Vagal manoeuvres
(caution possible digitalis toxicity, acute ischaemia or presence of carotid bruit)
Atrial fibrillation
(more than 130 beat min⁻¹)
Adenosine 3 mg by bolus injection repeat if necessary every 1–2 min using 6 mg then 12 mg then 12 mg
(ATP is an alternative)
Seek expert help
No
Yes
Adverse signs ?
• Hypotension
Systolic AP ≤ 90 mm Hg
• Chest pain
• Heart failure
• Impaired consciousness
• Rate ≥ 200 beat min⁻¹
Choose from.
• Esmolol 40 mg over 1 min + infusion 4 mg min⁻¹ (i.v injection can be repeated with increments of infusion to 12 mg min⁻¹)
• Digoxin: max. dose 500 μg over 30 min x 2
• Verapamil 5–10 mg i.v.
• Amiodarone 300 mg over 1 h, may be repeated once if necessary
• Overdrive pacing (not AF)
Sedation
Synchronized cardioversion
100 J 200 J: 360 J
Amiodarone 300 mg over 15 min then 300 mg over 1 h if necessary, preferably by central line and repeat cardioversion

Figure 3 Algorithm for narrow complex tachycardia

Vagal manoeuvres must be considered first, but they may not always be appropriate in peri-arrest situations: they are dangerous in the presence of acute ischaemia, with digitalis toxicity or in elderly patients, especially in those with a carotid bruit because of vulnerability to plaque rupture with cardiovascular complications.[4] Adenosine, however, is a comparatively safe treatment,[5] using rapid bolus administration at a starting dose of 3 mg, repeating every 1–2 min with increments to 6 mg, then 12 mg and, if necessary, a final second dose of 12 mg. Ideally adenosine is given into a central vein because its half-life is measured in seconds and a more peripheral injection may be inactivated before it reaches the coronary circulation. The injection should, in any case, be given as rapidly as possible. Even with central injections administered rapidly, severe circulatory impairment that slows the circulation may prevent an adequate concentration ever reaching the coronary circulation. If these simple treatments are unsuccessful, or if atrial fibrillation is identified, then expert help should be sought.

The factors that indicate adverse signs are similar as for broad complex tachycardia: hypotension (systolic pressure less than 90 mm Hg), heart failure and chest pain. But the list in this case includes impaired consciousness (which may occur without full cardiac arrest) or a rate of more than 200 beat min^{-1} (rather than 150 beat min^{-1} for broad complex tachycardia). In the presence of any of these signs the treatment should be by synchronized cardioversion using sequentially 100 J, 200 J and 360 J as necessary after appropriate sedation. If this fails amiodarone should be administered at an initial dose of 300 mg by central i.v. injection over 15 min, followed by 300 mg over 1 h. Spontaneous reversion may occur during the amiodarone infusion but otherwise repeat cardioversion should be attempted. If the need to reverse the arrhythmia is pressing, one or more shocks may be given during the amiodarone infusion. For refractory or recurrent atrial fibrillation, the slowing induced by amiodarone may relieve any haemodynamic compromise and be judged a satisfactory outcome. Occasionally controlled atrial fibrillation may be the most stable rhythm that can be achieved and may then be preferable to other recurrent supraventricular rhythms.

In the absence of adverse signs there is no one recommended "best buy". One reasonable choice may be esmolol[23] which is a short-acting beta blocker and can be used in a dose of 40 mg over 1 min (which may be repeated) with an infusion starting at 4 mg min^{-1} and increments as necessary to 12 mg min^{-1}. Digoxin may have a role either for the control of atrial fibrillation or for terminating some regular supraventricular tachycardias. The recommended dose is 500 μg over 30 min which can be repeated once. Verapamil is highly effective for narrow complex tachycardia in other situations but should be used with great caution in the peri-arrest situation, and is best reserved for the expert because there are circumstances in which its use is hazardous. These include arrhythmias associated with Wolff–Parkinson–White syndrome,[11] tachycardias that are ventricular in origin,[19] and some of the supraventricular arrhythmias of childhood.[18] The dose is 5–10 mg i.v. The dangers of interaction between verapamil and beta blocking agents is of particular concern if the drugs are used i.v.[9] Amiodarone may also be used, and in this context the appropriate dose is 300 mg over 1 h, repeated once if necessary. Overdrive pacing can also be effective but requires considerable expertise. It is not appropriate in the presence of atrial fibrillation.

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Fibrillation and defibrillation of the heart

L. L. BOSSAERT

Fibrillation is chaos[38 47 83 88 107]

Fibrillation of the atrium or ventricle of the heart is a result of chaotic electrical activity of the heart chambers, resulting in loss of coordinated myocardial contraction. Fibrillation of the atrium is characterized by loss of coordinated atrial contraction and by irregular conduction of this chaotic electrical activity through the A-V conduction system to the ventricles, leading to an irregular pumping pattern of the ventricles. Fibrillation of the ventricles is characterized by loss of coordinated ventricular contraction, leading to an immediate loss of pump function of the heart and causing cessation of blood flow and oxygen supply to the vital organs of the body. Loss of oxygen supply to the brain causes brain damage and eventually brain death after only a few minutes. This represents the pathophysiological substrate of sudden cardiac death (SCD).

The mechanism of initiation of ventricular fibrillation (VF) consists of the simultaneous presence of an arrhythmogenic substrate and a trigger. The substrate is usually an area of ischaemic myocardium or an ischaemic border zone surrounding an infarcted area. The substrate becomes increasingly vulnerable (decreased fibrillation threshold) by increased concentrations of circulating catecholamines, sympathetic imbalance, metabolic abnormalities, proarrhythmogenicity of drugs, and hyper- and hypothermia. The final trigger is usually an early ventricular premature ectopic beat (VPB). Coexistence of abnormal initiation of ventricular beats (increased excitability of the substrate, latent pacemaker activity) and abnormal propagation of the impulse (bradycardia, intraventricular conduction blocks, re-entry phenomena) generate chaotic electric activity in the presence of a lowered fibrillation threshold. An increase or marked slowing of heart rate are predisposing factors in the initiation of VF. When this chaos is present in a critical mass of ventricular myocardium, fibrillation invades the whole ventricle causing VF.

In the initiation of VF, a so-called "R-on-T" extrasystole is an important factor; late cycle ectopic ventricular tachycardia and idioventricular rhythm initiate VF less frequently.

Aetiology and epidemiology of VF

Primary VF (in the absence of shock or cardiac failure) occurs in the first 5–10 min after the onset of coronary occlusion and is usually induced by an early R-on-T VPB and only rarely by degeneration of ventricular tachycardia. The success rate for resuscitation of patients in the first minute of primary VF is probably 90–95%.[2 21 75]

Data on Holter monitoring have demonstrated that VF waves initially have a large amplitude of >0.2 mV and a median frequency of ±200–300 bpm. Progressively, rate and amplitude decrease and after approximately 12–15 min, fibrillation waves fade to become a flat isoelectric line.[13 53 64]

Secondary VF occurs in the presence of shock or cardiac failure and is caused by a variety of mechanisms, including dilatation, stretching, metabolic disorders, sympathetic overactivity and proarrhythmogenicity of drugs. Secondary VF has a far lower prognosis for successful resuscitation, with less than 30% success rate.

Ischaemic heart disease (IHD) is by far the principal cause of VF. More than 30% of all patients with acute myocardial infarction die from VF within the first 2 h after onset of symptoms. The majority of patients presenting with SCD caused by VF are those at risk of IHD (i.e. middle-aged men with other signs and symptoms of IHD). However, SCD caused by VF is not infrequently the first, and lethal, symptom of IHD.

Ischaemia and reperfusion are associated with life-threatening arrhythmias, but only 20% of SCD victims have an acute myocardial infarction. Therefore, transient ischaemia and reperfusion rather than infarction have major roles in triggering the arrhythmias leading to SCD.[39 91]

Other causes of SCD induced by VF include diseases of the heart (reperfusion, heart failure, congenital heart disease, cardiomyopathy, valvular, infiltrative and infectious disorders), transient autonomic and neurohumeral factors, toxic and proarrhythmic effects of drugs, hypothermia, electrolyte and metabolic disorders, hypoxia, hypotension and electric shock. In young subjects

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Key words
Heart, resuscitation. Heart, arrhythmia, fibrillation. Equipment, defibrillators. Complications, cardiac arrest.

LEO L. BOSSAERT, University of Antwerp UIA, Universiteitsplein 1, b-2610, Antwerp, Belgium.

(age <40 yr) cardiomyopathy and toxic substances are more important aetiologies than IHD.

Epidemiological investigation (European Monica registry) showed that the incidence of SCD caused by VF was approximately 1 per 1000 inhabitants per year. The incidence is higher in Northern countries and lower in Mediterranean countries. This lower incidence of IHD is believed to correlate with a different nutritional profile (the "French paradox").[20 97]

In common with other symptoms of IHD, the time of onset of VF has a circadian distribution pattern with a relative high risk during the day and the highest peak in the first 3 h after awakening. This time variation is believed to correlate with the degree of sympathetic instability and related biochemical variations.[7 71 96]

VF and the chain of survival

Survival after pre-hospital cardiac arrest is more likely when activation of the emergency medical services (EMS) system, basic cardiopulmonary resuscitation (CPR), defibrillation and advanced care occur as rapidly as possible. Implementation of these various elements of CPR in the treatment of cardiac arrest can be described best by the concept of "chain of survival". This concept illustrates that failure or weakness of any one of these links is associated with poor results. The concept of chain of survival describes each link in the EMS continuum that is needed for survival in cardiac arrest.[5 30 72]

- The first link in the chain of survival, "early access", is essential to bring trained persons and appropriate equipment quickly to the patient, includes recognition of the collapse, decision to call, calling and dispatch, and is strengthened by public education and availability of an efficient emergency communication system (including a unique simple telephone number for medical emergencies).
- The importance of the second link, "early CPR", by the first person witnessing the arrest (lay person or bystander health care worker) has been well documented. Bystander CPR can maintain the heart in VF for approximately 10–12 min longer. Basic CPR can sustain life until arrival of trained personnel with equipment and is therefore a bridge to defibrillation.
- The most crucial link is "early defibrillation". Initially, pre-hospital defibrillation was performed only by medical and paramedical staff, but recently newer and reliable technology has allowed the defibrillator to be used by first-line technician ambulance personnel. This strategy is of greatest value as long as the preceding links of the chain of survival do not fail. In systems where access time is excessively long, the results of an early defibrillation programme may be disappointing.
- The fourth link, "early advanced life support", implies early intervention of a well-trained and equipped team, working with specially equipped ambulances or rapid intervention vehicles. These teams consist of paramedics (in the USA, UK and Scandinavia) or trained ambulancemen, doctors and/or nurses (in most European countries).

VF and defibrillation

In the event of VF, electrical defibrillation is the only effective method of terminating the rhythm disturbance and restoring a perfusing cardiac rhythm. Landmark investigators include Zoll and colleagues,[112] Dahl and colleagues[34] and Pantridge, Adgey and Webb.[86] The success of electrical defibrillation is dependent on time and the metabolic state of the myocardium. The chances of successful defibrillation decrease rapidly over time, at a rate of more than 5% per minute. After a few minutes, the amplitude and frequency of the VF waveform decreases and after approximately 15 min degenerates into asystole, probably because of depletion of myocardial high energy phosphate reserves. The presence of asystole usually indicates that the time since collapse has been prolonged.[16 17 22 25 60 93 102]

MECHANISM OF DEFIBRILLATION

External defibrillation of the heart involves delivering an adequate electrical current flow through the heart, via electrodes applied to the chest wall, causing simultaneous depolarization of all myocardial cells that are at that moment fully refractory. Defibrillators consist of a power source (battery, AC source), voltage selector, AC–DC converter, capacitor and electrodes.[11 15 35 46] The output energy of the defibrillator is usually expressed in energy, where:

$$\text{energy (J)} = \text{power (W)} \times \text{duration (s)}$$

$$\text{power (W)} = \text{potential (V)} \times \text{current (A)}$$

$$\text{current (A)} = \text{potential (V)/resistance or impedance } (\Omega).$$

The output waveform of most conventional external defibrillators is half sinusoidal (damped Edmark waveform). The optimum duration of the power wave is 4–12 ms.

After defibrillation, myocardial contraction is re-established within minutes, but initially cardiac output may be extremely low, especially after prolonged VF, and continues to increase over minutes or even hours. This phenomenon has been described as the post-countershock pulseless rhythm or post-countershock myocardial depression.

Inspired by the work of Russian investigators and by the experience of implanted automatic defibrillators, the use of biphasic or triphasic waveforms has been advocated. Indeed, post-countershock dysfunction of the myocardium appears to depend on shock waveform. The defibrillation threshold seems to be lower using biphasic waveforms and causes less myocardial dysfunction with implantable defibrillators. Others have suggested that the biphasic waveform may reduce the defibrillation threshold by prolonging refractoriness which may protect ventricular cells from refibrillation wavefronts. The clinical relevance of biphasic waveform defibrillation at different energy levels is being investigated.[12 49 109]

TRANSTHORACIC IMPEDANCE: THRESHOLD AND ENERGY REQUIREMENTS

Not all cases of VF can be defibrillated by an external shock. The minimum shock strength capable of abolishing fibrillation is defined as the defibrillation threshold. The defibrillation threshold is influenced by anatomical variations in heart size, ventricular filling and lung volumes, and electrical variables such as defibrillation waveform and metabolic state, and biochemical and physiological differences in temperature, tissue pH and $P\text{O}_2$, extracellular potassium concentration, ischaemia and drugs. The energy requirement for defibrillation increases with the duration of fibrillation. The sum of these variables can be responsible for a five-fold difference in threshold as time elapses.[37 59 77]

In VF/tachycardia, defibrillation is accomplished by passage of sufficient electrical current through the heart to depolarize a critical mass of myocardium. The amount of current flowing through the heart depends on the energy of the shock and transthoracic impedance. During transthoracic defibrillation in humans, as little as 4% of the delivered transthoracic current traverses the heart because parallel pathways (thoracic cage, lungs) divert the current away from the heart.[33 74]

Transthoracic impedance depends on many factors: time to defibrillation; electrode size, contact, pressure, and distance from the heart; previous shocks; and ventilatory phase. The success of defibrillation depends not only on threshold but also on probability.

Defibrillation at too high energy levels can be proarrhythmic and cause functional and morphological damage to the myocardium. Shocks below the defibrillation threshold are ineffective and harmful because they may re-initiate VF by stimulating parts of the myocardium during a vulnerable period.[82 95 108]

Prospective clinical investigations have demonstrated that the success of defibrillation and subsequent hospital discharge rates were almost identical in patients receiving an initial shock of 175 or 320 J. Therefore, the energy selected for the first shock is a compromise between probability of success and risk of damage.[58 66 101] Based on this scientific evidence, the following guideline has been accepted widely for defibrillating an adult presenting with VF: first shock—200 J; second shock—200–300 J; subsequent shocks ≤360 J.

In children, a weight-related initial energy of $2\ \text{J kg}^{-1}$ is recommended.[50]

The average human transthoracic impedance is 70–80 Ω, but can occasionally be as high as 150 Ω and as low as 15 Ω. The energy for the first shock can be predicted and adjusted based on automatic measurement of impedance, and inappropriate low energies can be avoided in patients with high impedances.[67] This facility is already available in modern equipment

INFLUENCE OF DRUGS ON FIBRILLATION AND DEFIBRILLATION THRESHOLDS

Intervention studies have demonstrated that some routinely used drugs are proarrhythmic, serving only to aggravate the situation.[8 41 45 51 52 54 61 65 68 70 73 81 85 89 90 98 100] The pharmacological profiles of bretylium, amiodarone and beta-blocking drugs are probably superior to other commonly used antiarrhythmics in the treatment of VF refractory to countershock (table 1). Bretylium and lignocaine increase the fibrillation threshold significantly. However, lignocaine also increases the defibrillation threshold whereas bretylium does not. Lignocaine in association with acidosis produces a further increase in the energy required; respiratory alkalosis causes a reduction in energy required to defibrillate successfully. Administration of lignocaine during myocardial reperfusion in CABG allows defibrillation with fewer DC shocks of lower energy and current. Bretylium lowers the defibrillation threshold in dogs and facilitates conversion of hypothermia-induced VF. However, deleterious effects of bretylium on haemodynamic recovery from VF have occasionally been reported.

Table 1 Pharmacological profiles of antiarrhythmic drugs

Drug	Fibrillation threshold	Defibrillation threshold	Proarrhythmogenicity
Quinidine	++	+++	+
Procainamide	++	0	+
Encainide	++	+++	+
Flecainide	++	+++	+
Lignocaine	++	+	+
Bretylium	++	−	+
Amiodarone	++	−	0/+
Verapamil	+	++	0
Diltiazem	+	++	0
Nifedipine	+	0	0
Adrenergic agents	−	0	+
Beta-blockers	++	+	0
Sotalol	+	−	+

The effect of other antiarrhythmic drugs is less clear (table 1): procainamide has no effect on defibrillation energy requirements. Flecainide significantly increases the defibrillation threshold and has adverse proarrhythmic and haemodynamic effects in dogs. Propafenone reduces energy requirements for defibrillation in pigs.

The calcium channel blocking drugs, diltiazem and verapamil, increase the defibrillation threshold, whereas nifedipine and nisoldipine do not.

Adrenaline has no effect and propranolol increases the defibrillation threshold. Beta stimulation decreased the defibrillation threshold significantly in dogs, an effect that was blocked by propranolol. Sotalol (DL and D) decreased defibrillation energy requirements.

Excessive administration of magnesium may increase the defibrillation threshold.

PRACTICAL CONSIDERATIONS

Paddle size, shape and position

Electrode pad size is an important determinant of transthoracic current flow during external countershock. Larger self-adhesive electrocardiogram/defibrillator pads are associated with a lower transthoracic impedance and improved defibrillation success rates with low energy shocks. The optimum electrode size is ±13 cm in diameter in adults, 8–10 cm in children and 4.5–5 cm in infants.[10 36] There has been no attempt to standardize the physical characteristics of adhesive pads for automated external defibrillators.

Paddle position influences current flow through the myocardium. One electrode should be placed below the outer half of the right clavicle and the other just outside the usual position of the cardiac apex (V4–5 position). Anterior–posterior (one paddle over the precordium and the other on the back just behind the heart) electrode placement may be recommended in patients with implanted defibrillators or pacemakers. The influence of polarity on the defibrillation threshold is negligible.[103]

Disposable coupling pads are as effective as electrode paste.[11] Jelly is probably less satisfactory as it tends to be spread across the chest wall during resuscitative efforts: the shock then arcs across the chest wall, failing to reach the heart in adequate strength.

Before performing external defibrillation, all nitro patches and ointments should be removed from the chest wall.[110]

External defibrillation and pacemakers

Pacemaker problems reported during external defibrillation include transient malfunctions of pacing, capture and sensing. Although modern pacemakers are less likely to be disturbed by external defibrillation, an increase in pacemaker threshold has been described. With implanted pacemakers, anterior–posterior electrode or paddle placement maintaining a distance of 12–15 cm from the pacemaker module is recommended. Pacing functions should be checked immediately in patients who have been defibrillated.[69 80 113]

Technical problems

In a review of more than 2100 technical reports related to defibrillator problems, some failures were attributable to component malfunctions, but errors in operator use and defibrillator care and maintenance accounted for the majority of defibrillator failures. Where defibrillators are used relatively frequently, such as in ambulances, emergency departments, intensive and coronary care units, operating theatres and catheterization laboratories, it is recommended that the operational state of the equipment is assessed every day using appropriate checklists.[29] Inadequate training and re-training increase the chances of operator errors at the critical moment.

Resuscitation algorithm for VF

Based on the available scientific knowledge, a universal algorithm for the advanced life support (ALS) management of VF patients has been proposed by the International Liaison Committee on Resuscitation (ILCOR) (fig. 1). This committee includes representatives from the European Resuscitation Council, American Heart Association, Canadian Heart and Stroke Foundation, Australian Resuscitation Council and Southern African Resuscitation Council.[13 44 94]

After confirmation of cardiac arrest, a precordial thump should be given immediately and the defibrillator pads applied. The diagnosis of VF should be followed immediately by three electric shocks of 200, 200–360 J, without interposed CPR. After the initial three shocks, the airway should be secured and i.v. access achieved, if these manoeuvres have not already been performed. At this stage adrenaline 1 mg i.v. should be given (2.5 mg if given by tracheal tube), and 10 sequences of five chest compressions: one ventilation should be given.

The next shocks should be given as quickly as possible and the interval between the third and next (fourth) shock should not exceed 2 min: the more rapid a coordinated rhythm is restored, the better the prospects of long-term success. In patients whose trachea is intubated, the next shock should be given immediately after the 10 CPR cycles have been completed and adrenaline was given, and tracheal intubation should be aborted temporarily if unsuccessful after approximately 30 s.

The fourth shock forms the beginning of a new sequence of three shocks. Additional doses of adrenaline 1 mg may be given at less than 2-min intervals (fig. 1).

Automated external defibrillator (AED)

The most frequent initial rhythm in SCD is VF. The most effective treatment for VF is electrical defibrillation; the probability of successful defibrillation diminishes rapidly over time and VF tends to convert to asystole within a few minutes. The rationale of AED programmes is to reduce the time to first defibrillation.

Originally, defibrillation could only be performed by emergency care providers who were trained in ALS. Today it is often performed by lesser trained BLS personnel. AED eliminates the need for training in rhythm recognition and makes early defibrillation by untrained personnel practical and achievable.

The first automated implantable defibrillators were developed by Mirowski in 1970. In the past 40 yr, external defibrillation has become the most important tool for termination of lethal arrhythmias. The first successful defibrillation of ventricular fibrillation outside hospital was achieved by the Belfast Mobile Coronary Care Unit in 1966 and the first automated defibrillators appeared in Brighton in the late 1970s.[56 57]

SOME TECHNICAL NOTES ABOUT AED

Automated defibrillators are now available for use primarily outside hospital. The terms automated and shock-advisory defibrillators refer to external defibrillators that incorporate a rhythm analysis system. AED are attached to the patient by two adhesive pads with connecting cables to analyse the rhythm and deliver the shock. The information is given by voice or a visual display, or both, and the

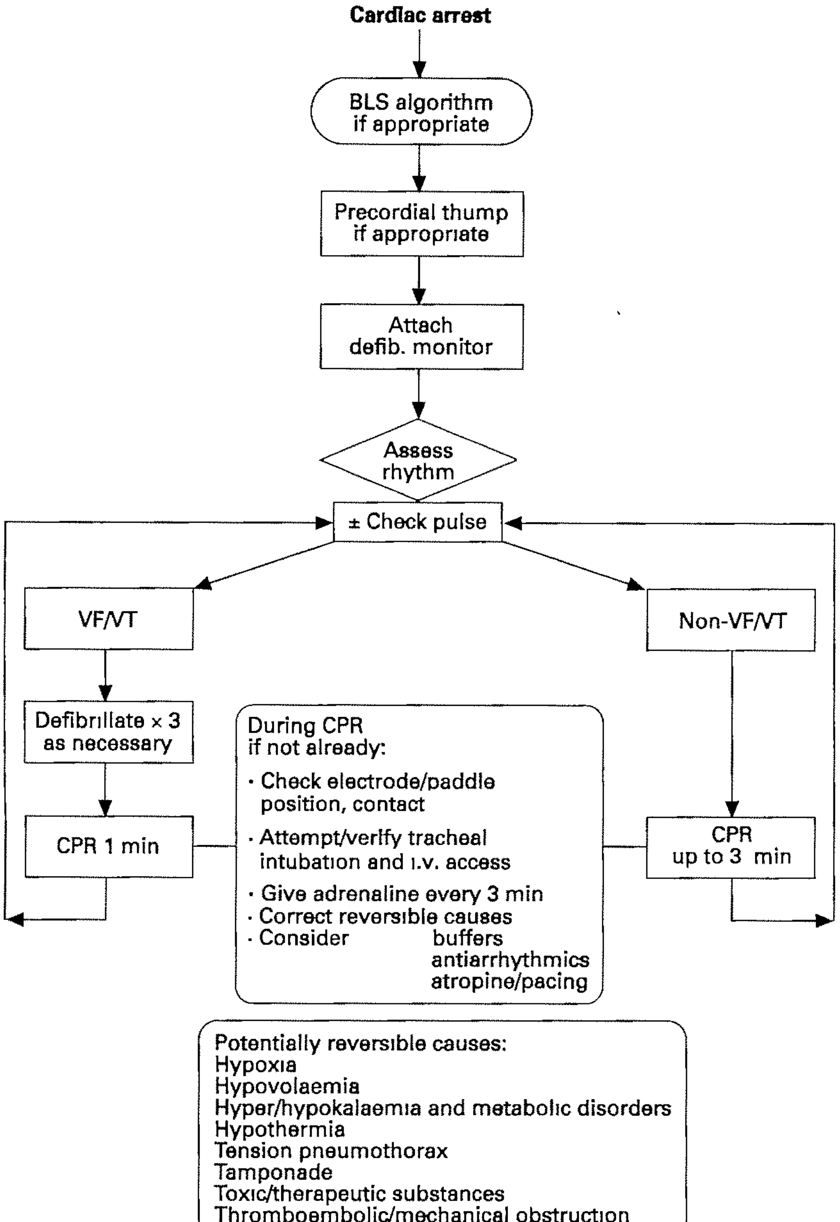
Cardiac arrest
BLS algorithm if appropriate
Precordial thump if appropriate
Attach defib. monitor
Assess rhythm
± Check pulse
VF/VT
Non-VF/VT
Defibrillate × 3 as necessary
CPR 1 min
CPR up to 3 min
During CPR if not already:
· Check electrode/paddle position, contact
· Attempt/verify tracheal intubation and i.v. access
· Give adrenaline every 3 min
· Correct reversible causes
· Consider buffers antiarrhythmics atropine/pacing
Potentially reversible causes:
Hypoxia
Hypovolaemia
Hyper/hypokalaemia and metabolic disorders
Hypothermia
Tension pneumothorax
Tamponade
Toxic/therapeutic substances
Thromboembolic/mechanical obstruction

Figure 1 Adanced life support (ALS) algorithm for the management of cardiac arrest in adults. Note that each successive step is based on the assumption that the one before has been unsuccessful.[56]

actual delivery of the shock is triggered manually.

These systems have great potential for use by basic ambulance men who may not be trained in ECG interpretation. Although specificity for VF is approximately 100%, sensitivity for coarse VF is approximately 90–92%, for fine VF even lower and for VT only 50%.[23 32 87]

Moreover, in patients with an implanted automatic defibrillator, failure of the diagnostic algorithm has been documented when the patient also has an implanted pacemaker.[80]

The present equipment is relatively expensive, and performance is dependent on good maintenance.[4] A new generation of AED are now appearing on the market using new battery technology and some also have new waveform technology. They are small, simple, reliable and less expensive. Some of the new devices have the facility for ECG display. These new generation AED will stimulate widespread availability of defibrillators in ambulances, doctor's cars, places of work, public places, aeroplanes and cruise ships, etc.

EARLY DEFIBRILLATION BY FIRST-RESPONDING AMBULANCE PERSONNEL

Electrical defibrillation is the only effective therapy for VF. The chances of successful defibrillation decrease rapidly over time by more than 5% per minute. It has been demonstrated in Belgium and Sweden that bystander CPR can maintain the heart in VF longer, for approximately 10–15 min, and is therefore a bridge to first defibrillation.

In two-tiered EMS systems, the first ambulance generally arrives several minutes before the second ambulance, which usually has the defibrillator and medically qualified personnel on board. The Belgian CPCR registry showed that 69% of cardiac arrest

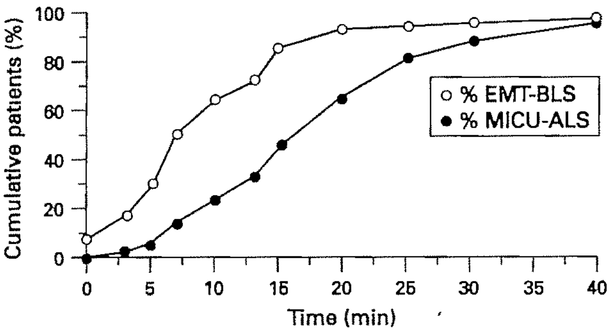

Figure 2 Cumulative inclusion of cardiac arrest patients by the first-tier ambulance (EMT-BLS) and by the second-tier ambulance (MICU-ALS), illustrating that the first-tier arrives significantly faster than the second tier.[19]

patients were first attended by the basic ambulance manned by two EMT; the median time interval between collapse and start of BLS resuscitation by the EMT was 8 min; the median time interval between collapse and defibrillation by the second-tier medical ALS team was 16 min. It was concluded that EMT can be expected to reach a substantial number of VF victims within a few minutes after collapse and many minutes before arrival of the medical ALS team (fig. 2).[19]

Therefore, it seemed logical to equip first-tiered ambulances with defibrillators and to train first-line ambulancemen in the use of AED. The expected result is that EMS systems, based on early defibrillation by first-line ambulancemen, will provide not only shorter times to initial countershock but also, by having delegated initial defibrillation to first responders, they will produce significantly shorter times to i.v. access, tracheal intubation and initial adrenergic drug therapy.[55]

AED training

Experiences in Scandinavia, the UK, Germany, Belgium and the USA have demonstrated that a training course of less than 8–10 h followed by 6-monthly refresher courses is sufficient to instruct an ambulanceman in the correct use of an AED according to a standard procedure. Knowledge of basic CPR is a prerequisite for successfully attending an AED course.

The AED training course and subsequent implementation of an AED programme, should be placed under full medical supervision. The course should include background information, knowledge of the equipment and its maintenance, and knowledge of the procedure, and should be tested by an examination. Formal 6-monthly refresher courses are needed, with feedback to discuss each intervention.

To achieve the goal of early defibrillation, ideally all emergency personnel responding to cardiac arrest should be trained, equipped and permitted to defibrillate.

Following the early pre-hospital experience in Belfast and Brighton, defibrillator technology has been developed further and systems are now implemented in many countries in a community wide basis. Early defibrillation with AED by ambulance personnel is now available widely in the UK and Scandinavia, and in parts of Germany and Belgium. Pilot studies are emerging in many European countries: France, Spain, Italy, Austria, Switzerland. In the Netherlands and Spain, all ambulances are manned by experienced nurses or doctors, or both, and are equipped with manual defibrillators.

As a result of these experiences it has been recognized that the success of an early defibrillation programme depends on the following factors:

- the programme should be placed under medical control
- the majority of arrests should be witnessed
- the time interval between cardiac arrest and first CPR should be <4 min
- the time interval between cardiac arrest and defibrillation should be <12 min
- there should be a minimum number of interventions
- there should be a programme of training and retraining
- there should be a programme for monitoring the performance of the programme.

SLOW IMPLEMENTATION OF AED BY FIRST-RESPONDING AMBULANCE PERSONNEL IN EUROPE

AED programmes are only partially implemented in continental Europe. Important reasons for this slow implementation include: lack of motivation and awareness; organization of EMS systems; and legal issues. Moreover, in the USA, widespread implementation of AED programmes has also been delayed by regulatory authorities.[31]

Awareness

In Europe, cardiovascular disease accounts for more than 45% of mortality. However, public awareness is most influenced by information provided by the media. In a recent survey in a sample of the adult Belgian population, only 8% of respondents answered that cardiovascular disease was their major concern, whereas the values were 18% for traffic accidents and 17% for AIDS.[9]

Organization

In all European countries access to the EMS system is by a specific telephone number. The European Union has recommended the use of 112 as the uniform European emergency telephone number.[14 24 42 106]

There is a wide variety of European EMS systems: one-tiered systems delivering BLS by an EMT (basic ambulance person); one-tiered systems delivering BLS and defibrillation by an EMT-d; one-tiered systems delivering BLS and ALS by paramedics, doctors and/or nurses; two-tiered systems delivering BLS followed by ALS; and two-tiered systems delivering BLS and defibrillation, followed by ALS (table 2). Best performance, in terms of survival, is obtained with systems with highly qualified staff provided they are available quickly.

The structure and organization of the EMS

Table 2 EMS systems in European countries. Local variations in the country are indicated between brackets. md=medical doctor, rn=nurse; pm=paramedic; EMT=emergency medical technician; EMT-d=emergency medical technician qualified for use of AED (*)In the presence of a doctor. For permission to defibrillate, the minimum training level is mentioned

Country	1st tier	2nd tier	Emergency phone	Who is allowed to defibrillate
Austria	EMT	md	144	md, EMT (*)
Belgium	EMT-(d)	md	100	md, rn, EMT-d
Bulgaria	md	md	150	md, rn, EMT-d
Croatia	md	—	94	md
Czechia	EMT	md	155	md, pm
Denmark	EMT-(d)	(pm)	112	md, rn, EMT-d
Finland	EMT-(d)	md	112	Everybody trained
France	EMT	md	15	md, rn, EMT-d
Germany	EMT-(d)	md	112	md, pm, EMT-d
Greece	EMT	—	166	md
Hungary	EMT-(d)	rn/md	04	md, pm, EMT-d
Iceland	EMT-(d)	md	0112	md, EMT (*)
Ireland	EMT	—	999	md, rn, pm
Italy	EMT	(md)	118	md,rn
Netherlands	rn	—	06–11	md, rn
Norway	EMT-d	md/pm	113	md, EMT-d
Poland	md	md	999	md, EMT(*)
Portugal	md	—	115	md, EMT(*)
Romania	rn/md	md	06	md, rn
Russia	md	—	03	md/ representative
Slovakia	md/pm/rn	md	155	md, rn, emt-d, pm
Slovenia	md	—	94	md, rn, emt-d
Spain	EMT/rn/m	—	061	md, rn no law
Sweden	EMT-d	pm	90 000	md, rn, EMT-d
Switzerland	EMT	(md)	114	md, rn, pm
Turkey	md	—	118	md
UK	EMT-(d)	(pm)	999	No law
Yugoslavia	md	md	94	md, rn, emt

systems in European countries, and the legal background for defibrillation practice are summarized in table 2

In the majority of continental European countries, doctors have an active role in pre-hospital emergency medical care, as part of the first or second tier. In most parts of Scandinavia and the UK, paramedics serve as members of the first or second tier. This medical presence on the field could be a reason for slow involvement of ambulance personnel in defibrillation.

Legislation

Because of historical, organizational, political and religious reasons, legislation relating to resuscitation and defibrillation is different in European countries. In countries where historically only ambulancemen and paramedics were present in the field, implementation of early defibrillation by ambulancemen was easy. However, in countries where a medical presence was prominent in the second or even in the first tier, introduction of defibrillation by first-line ambulancemen was much slower.

Information on legal regulations has been collected from 28 European countries:

Providing help. In all European countries (except the UK, where there is no legislation), anyone is legally obliged to provide help to endangered persons.

Providing CPR. In 20 of 28 countries, anyone (or anyone who has been instructed) is legally allowed (or not forbidden) to start CPR. In five countries there is no specific legislation and in three countries CPR is restricted to health care professionals. In seven of 28 countries anyone who has been instructed, in 12 of 28 any health care professional (whether or not in an official capacity), and in four of 28 countries only doctors are legally obliged to start CPR. In five countries there is no specific legislation.

Providing defibrillation. In most European countries, defibrillation was considered until recently to be solely a medical intervention, which reflects the historical involvement of doctors in out-of-hospital emergencies and major incidents. In four of 28 countries the law restricts the act of defibrillation exclusively to doctors, and in five countries only nurses can be delegated to defibrillate. In six countries, ambulance personnel are allowed to defibrillate only in the presence of a doctor. In 11 of 28 countries defibrillation can legally be performed by nurses, paramedics or qualified health care professionals. In the UK and Spain there is no legal restriction on providing defibrillation. This means that in at least 10 European countries the law is an obstacle for nationwide implementation of AED programmes by non-physicians. In countries where nurses may be allowed to defibrillate, there is a potential problem for ambulances that are manned by EMT.

The cost of hardware is decreasing for new generation devices. Training and re-training are very demanding and require substantial effort and logistic solutions. Other major obstacles are public and political awareness, tradition and structure of the EMS systems, and motivation of the medical community. Increasing public and political awareness and increasing motivation in the medical profession can help to overcome these obstacles.

RESULTS OF AED PROGRAMMES OF EARLY DEFIBRILLATION BY FIRST-LINE AMBULANCE PERSONNEL

Reported data on survival after cardiac arrest caused by VF by non-medically qualified personnel using an AED, range from 4 to 31%.[6,26,43,48,63,78,79,92,99] These variations may be related to: differences in characteristics of the treated population; differences in methodology and quality of registration; and differences in the performance of the AED programme.

One of the key elements that determines success of an AED programme is the percentage of cardiac arrest patients found in VF, which is a reflection of the speed of intervention of the EMS system. Reported incidences of VF in different cities and countries around the world range from 62% to less than 10%. As expected, there is a significant correlation between the incidence of VF and subsequent survival. As a consequence, it is unclear if the reported differences in survival rates are a result of differences in system organization, treatment procedures or in the skills of the personnel.

The "Utstein style" presents a glossary of terms and reporting guidelines for description of cardiac arrest, resuscitation, the EMS system and outcome, and was published by representatives of the American Heart Association, the European Resuscitation Council, the Heart and Stroke Foundation of Canada, the Southern African Resuscitation Council and the Australian Resuscitation Council. The recommendations were published simultaneously in *Circulation*, *Resuscitation*, *Annals of Emergency Medicine* and other major journals. The in-hospital "Utstein style" has been published in 1997.[18,27,28]

IMMEDIATE DEFIBRILLATION BY FIRST-LINE TRAINED INDIVIDUALS

As considerable time may elapse between the onset of VF and arrival of the emergency medical services, immediate defibrillation by first-line trained bystanders may be the long-term realization of the concept of early defibrillation. A first responder is defined as a trained individual, acting independently within a medically controlled system.

Although immediate first-responder defibrillation is the logical theoretical next step after implementation of defibrillation by ambulance personnel, there is at present no evidence that bystander defibrillation increase survival rates. There have been occasional cases of defibrillation in-flight and in a railway station.

Programmes should be developed to test the principle that first responders assigned to the management of cardiac arrest in the community should be trained and permitted to defibrillate. This could include police, security officers, life guards, voluntary aiders and those assigned to provide first aid at their place of work. Every programme designed to implement first-line defibrillation should be evaluated critically to assess if first-line defibrillation increases survival.[40,62,76,84,104,105]

Conclusions

Cardiorespiratory arrest caused by sudden arrhythmia as a consequence of myocardial ischaemia or infarction continues to be a leading cause of unexpected death in the community. Increased public education in the recognition of early symptoms and signs of a heart attack is likely to achieve a significant reduction in the present mortality and morbidity of out-of-hospital heart attack.

Electrical defibrillation is the single most important therapy for the treatment of VF. The time interval between onset of VF and delivery of the first defibrillation shock is the main determinant of survival. This should be as short as possible. Early defibrillation has a crucial role in the chain of survival. To achieve the goal of early defibrillation, it is mandatory to allow individuals other than doctors to defibrillate. At present, however, early defibrillation by ambulance personnel using automated external defibrillation (AED) is not yet widely implemented.

Obstacles to implementation of AED by ambulance personnel are: legislation, structure of EMS system, economic priorities, awareness, motivation and tradition. It is also recognized that success of an early defibrillation programme is dependent on the following factors: the programme is placed under medical control; the majority of arrests are witnessed; the time interval between cardiac arrest and first CPR is usually <4 min; the time interval between cardiac arrest and defibrillation is usually <12 min; there is a minimum number of interventions; there is a programme of training and re-training; and there is a programme for monitoring the performance of the programme.

Recommendations

- The medical profession is urged to increase awareness of the public and of those responsible for emergency medical services and regulatory powers to permit changes in practice and legislation where necessary.
- It is essential to integrate the concept of early defibrillation into an effective emergency cardiac care system. This is best characterized by the "chain of survival" concept, which includes early access to the emergency medical services (EMS) system, early cardiopulmonary resuscitation when needed, early defibrillation when indicated and early advanced cardiac care.
- All *emergency personnel* should be trained and permitted to operate an appropriately maintained defibrillator if their professional activities require that they respond to persons experiencing cardiac arrest. This includes all first-line emergency personnel working in an organized EMS system, both inside and outside hospital (e.g. emergency medical technicians (EMT), non-EMT first responders, fire fighters, volunteer emergency personnel, physicians, nurses and paramedics).
- All emergency ambulances and other emergency vehicles that respond to or transport cardiac patients should be equipped with a defibrillator.
- Defibrillation should be a core competence of professional nurses, and defibrillators should be available widely on general hospital wards.
- All defibrillator programmes must operate within medical controls by qualified and experienced physicians. They should ensure that every link of the chain of survival is in place and should have access to all information required to permit system audit.
- To monitor the programme, there must be appropriate registration of the interventions according to the Utstein style.

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Immersion, near-drowning and drowning

F. ST C. GOLDEN, M. J. TIPTON AND R. C. SCOTT

"Drowning" is defined as "suffocation by submersion, especially in water"[66]; it continues to be the third most common cause of accidental death in the general population and, for children in many countries, the second most common cause after road accidents.[75] In the USA, 40% of drowning victims are less than 4 yr old.[74] In Britain, the Office of Population Census reports that child deaths from this cause continue to be the third most common cause of accidental death after road accidents and burns.

"Near-drowning" is defined as "survival, at least temporarily, after suffocation by submersion in water".[65] We would challenge this definition as most dictionaries define "suffocation" as cessation of breathing leading to *unconsciousness* or death. However, pulmonary complications may follow aspiration of water without cessation of breathing or loss of consciousness. Thus "near-drowning" should be defined as "survival, at least temporarily, after aspiration of fluid into the lungs". The importance of the distinction between the two definitions is that aspiration of fluid may lead to later pulmonary complications, even in those *without* a history of loss of consciousness, and thus care must be exercised in the management of *all* patients with a history of aspiration. Modell, Graves and Ketover reported[68] that in dogs, aspiration of as little as 2.2 ml/kg body weight produced a decrease in Pa_{O_2} to approximately 8 kPa (60 mm Hg) within 3 min. Pulmonary surfactant is altered locally by water in the alveoli resulting in pulmonary shunting via either fluid-filled (salt water) or atelectatic (fresh water) alveoli. Pearn[78] stated that within minutes after inhalation of as little as 2.5 ml/kg body weight, the normal intrapulmonary shunt of approximately 10% may increase to as much as 75%. Even victims who are conscious, alert and outwardly clinically normal after a near-drowning incident may take several days to revert to pre-immersion values.[78] After aspiration of either fresh or salt water there may be delayed outpouring of fluid into the alveoli, secondary to pulmonary parenchymal damage with transudation of protein rich fluid, so called *"secondary drowning"*,[77,82] with consequent impairment of gas exchange. Orlowski[74] cited several cases who appeared normal on assessment in the emergency department, even with normal chest x-rays, but who developed fulminant pulmonary oedema as long as 12 h after the near-drowning incident.

While statistics on the incidence of drowning deaths are available for most nations, there are no precise data for near-drowning incidents, although in the USA they are estimated to be 500–600 times more common than their fatal counterpart.[75] In Britain, a comprehensive hospital survey for the years 1988–1989 by Kemp and Sibert[53] of 330 drowning and near-drowning incidents in children reported 142 deaths and 188 survivors.

One of the great tragedies of drowning or near-drowning is that the victims, frequently young, are generally in good health before the unexpected event which resulted in death or brain damage in a number of survivors. In recent years increased public awareness of the general principles of basic life support and cardiopulmonary resuscitation (CPR) has resulted in many more near-drowning victims arriving in hospital in a state capable of being resuscitated. The many contemporary reports in the literature of apparently hopeless cases being successfully resuscitated, particularly after cold water submersion,[11,20–22,38,45,53,54,59,85,86,102] has led to protracted resuscitative efforts by hospital personnel.

Drowning and near-drowning have been the subject of many reviews.[15,64,66,74,78,88] While resuscitation and the subsequent respiratory management of the near-drowning patient is now well established and largely non-controversial, the remaining major therapeutic challenge is limitation of brain damage in survivors with its associated consequent human and economic costs. Although the success stories tend to be reported, in the absence of full statistical information it is difficult to obtain an overall picture of the ratio of those who have been resuscitated and left with or without residual brain damage.

The criteria used to identify those with a poor prognosis needs to be refined. Some centres, based on retrospective analysis, have reported their results of various treatment regimens with suggested predictive criteria for recovery without severe brain damage.[34,53,68,74] Regrettably, these criteria are often

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F. ST C. GOLDEN, MB, BCH, PHD, M. J. TIPTON, MSC, PHD, Robens Institute, University of Surrey, Guildford, Surrey GU2 5XH. SURGEON COMMANDER R. C. SCOTT, MB, BSC, BCH, FRCA, Royal Navy, RH Haslar, Gosport, Hants PO12 2AA.

conflicting and thus of little real value other than to act as a reminder that long-term complications occur and caution should be exercised in discussing prognosis with relatives in the early stages. One of the problems appears to be that, although the protective role of hypothermia is now generally recognized, it is not always possible to determine from deep body temperature on arrival at hospital what the cerebral temperature was before severe hypoxia developed.

This review examines the physiological considerations of accidental immersion and discusses the factors which may influence outcome. The recommended management of such victims is also reviewed, with particular emphasis on the role of cardiopulmonary bypass.

Physiological considerations

IMMERSION IN THERMONEUTRAL WATER

The physiological effects of immersion in thermoneutral water have been reviewed previously by Epstein.[24] In sum, changes which occur are largely a consequence of the effects of the external hydrostatic pressure on the resilient body tissues and gas-containing body cavities during head-out immersion. This results in physiological alterations in the cardiovascular and respiratory systems, and in the gastrointestinal tract. The increase in venous return causes a 32–66% increase in cardiac output, increase in right to left shunting as a result of a combination of pulmonary pooling, cephalic movement of the diaphragm and, to a lesser extent, minor compression of the chest wall; overall there is a 65% increase in the work of breathing. The central shift in blood volume is sensed by the body as hypervolaemia and results in diuresis, natriuresis and kaliuresis.[25]

From a practical viewpoint there is little evidence that these changes cause respiratory or circulatory embarrassment in a healthy individual.[61] However, during rescue, after protracted immersion in warm water, or relative shorter immersion in cold water when hypothermia may be present, circulatory collapse and cardiac arrest may occur. This phenomenon, which has been termed "circum-rescue collapse" is considered to be outside the scope of this article and has been reviewed elsewhere.[32]

IMMERSION IN COLD WATER

The increase in right atrial pressure, resulting from reflex peripheral cold vasoconstriction after immersion in cold water, is additive to the hydrostatic pressure effect described above and enhances urinary output by as much as one-third.[55] However, of more importance to the accidental immersion victim are a group of cardiorespiratory reflex responses which can occur on sudden immersion in cold water and last for approximately 2–3 min. These responses, collectively known as the "cold-shock" response, have been reviewed by Tipton.[91] They are initiated by a rapid decrease in skin temperature and are probably responsible for the majority of near-drowning incidents and drowning deaths after accidental immersion in open waters in the UK. Respiratory drive is enhanced on immersion in water colder than 25 °C[52] and is inversely related to water temperature, reaching a maximum level with immersion in water at 10 °C.[96] The response includes an initial "gasp" of 2–3 litre in an adult, followed by uncontrollable hyperventilation which can result in a 10-fold increase in minute ventilation[93] which significantly reduces Pa_{CO_2}.[51] The inspiratory shift in end-expiratory lung volume after cold water immersion can result in tidal breathing within 1 litre of total lung capacity, creating a sensation of dyspnoea. This, coupled with the swim stroke/respiration asynchrony caused by hyperventilation, makes swimming very difficult, and is believed to be one of the major causative factors in the mechanism of cold-water swim failure.[31]

The maximum breath-hold times of normally clothed individuals are reduced to less than 10 s.[92] As a consequence, on immersion in choppy or turbulent water where the airway may be intermittently submerged, there is a significant chance of aspiration during the first few minutes. Breath-holding to facilitate escape from a submerged vehicle may be equally difficult and result in entrapment and drowning, or possibly near-drowning in those who manage to escape or are rescued before a lethal volume of water is aspirated, approximately 22 ml kg^{-1}.[68]

The initial cardiovascular responses to cold immersion include an immediate intense reflex peripheral vasoconstriction, 42–49% increase in heart rate and 59–100% increase in cardiac output,[40] with a resulting increase in arterial and venous pressures. These responses significantly increase the workload of the myocardium and, coupled with the concomitant increased catecholamine response,[5 16 48] may induce undesirable cardiac arrhythmias.

Thus in healthy young people, who may be competent swimmers but unhabituated to cold, the initial respiratory responses to immersion in cold water may cause short-term incapacitation which could prevent them from relaxing and swimming a short distance to save their lives. In turbulent water, or if escape from a submerged vehicle is necessary, the inability to breath-hold for more than 10–20 s may result in aspiration and near-drowning, or even drowning.

Additionally, in middle-aged or elderly people with heart disease, hypertension or vascular disease, the initial cardiovascular responses to immersion in cold water may precipitate a cardiovascular accident. It is considered that this mechanism as a cause of incapacitation resulting in drowning is probably underestimated. The eyewitness reports of the sudden cessation of movement in some drowning victims[66] is more suggestive of sudden circulatory malfunction. The fact that aspiration may occur subsequent to a cardiovascular incident may mislead some into concluding that drowning was the only problem requiring treatment or the cause of death.

Given the above, it is perhaps less surprising to discover that 60% of the annual open water immersion deaths in the UK occur within 3 m of a safe refuge, and two-thirds of those who die were regarded as "good swimmers".[44]

HYPOTHERMIA

"*Hypothermia*", defined as a deep body temperature <35 °C,[81] is an inevitable consequence of protracted immersion in cold water and appears to play an important role in the successful outcome of those who have survived prolonged submersion. The mechanism of how deep body temperature is reduced so rapidly in some of these victims is less clear.

The rate of change of core temperature in an immersed body is dependent on the inter-relationship of several physical and physiological factors such as water temperature, relative movement of water adjacent to the skin, body surface area to mass ratio, insulation, peripheral circulation, metabolism or conditions which may affect any of these factors (e.g. injury, intoxication, etc).

With continued body cooling, consciousness becomes progressively impaired until it is lost at a deep body temperature of approximately 30 °C.[17] Cerebral blood flow decreases in proportion to the reduction in metabolism,[42] while Stone, Donnelly and Frosbese[89] reported a 6–7% reduction for each decrease in core temperature of 1 °C; cerebral activity is abolished at brain temperatures less than 22 °C.[1] However, these data relate to anaesthetized patients in whom shivering was controlled. In victims of accidental immersion in cold water whose airway is being maintained clear of the water by a life jacket, shivering is pronounced with a resulting increased production of carbon dioxide, at least in the early stages, until body temperature decreases to approximately 29 °C. Should ventilation be impaired however, shivering is depressed or even absent while hypercapnia produces cerebral vasodilatation which increases cerebral perfusion.

With further cooling, in spontaneous breathing adults, cardiac arrest from ventricular fibrillation (VF) may occur at a deep body temperature <28 °C, or asystole at approximately 24–26 °C.[3] However, with surface cooling, when core temperatures decrease to 35–33 °C, skeletal muscle temperatures are usually at or below 28 °C when neuromuscular performance is significantly impaired, making swimming or other actions necessary for survival extremely difficult.[94] Therefore, it is likely that most immersion victims, excepting those wearing a life jacket with a "spray hood",[28] aspirate water as consciousness becomes impaired (i.e. as core temperature decreases to less than 34 °C) and thus well before significant protection from cerebral hypoxia is bestowed.

In spite of the ability of cold water to extract heat from the immersed body, hypothermia *per se* is unlikely to be a problem within 30 min of head-out immersion for a healthy, clothed adult, even in water as cold as 5 °C. The normal physiological responses to cold reduce heat transfer by mass flow (circulation) to the surface from the deeper tissues and increase shivering heat production by as much as five-fold.[30] As a general rule, however, in spite of these responses, during head-out immersion in laboratory conditions, deep body temperature of the average adult wearing outdoor clothing has fallen to 35 °C after approximately 1 h in water at 5 °C, 2 h in water at 10 °C, and 3–6 h in water at 15 °C.[94] In open water however, because of the rich supply of blood vessels to the scalp which do not vasoconstrict in the cold, heat loss from the unprotected head may be enhanced by forced convection and evaporation thereby increasing the rate of body cooling considerably. Similarly, if the head is immersed the rate of body cooling is significantly faster.

Because of their greater surface area to mass ratio and reduced subcutaneous fat content, cooling rates of immersed children are also significantly faster than those seen in adults. However, with surface cooling alone, even in children, rates for decrease in body temperature are too slow to cool the brain sufficiently to protect it from the hypoxia encountered in drowning asphyxia. In anaesthetized naked infants, being surface cooled for surgery with ice packs and ice cold water, rectal temperatures decreased by as little as 2.5 °C in the first 10 min of the procedure, and it took 32.5 min for it to reduce to 24–25 °C.[70] Thus if cerebral hypothermia is the mechanism through which some children can survive protracted submersion without sustaining lasting hypoxic neurological damage, an alternative method of heat exchange to surface cooling alone must be found.

To date it has been postulated by several authors[23 29 33 35 59 71 78 86] that the "mammalian diving response", either alone or in combination with hypothermia,[33] may be the explanation.

DIVING RESPONSE

The diving response, characterized by apnoea, generalized marked peripheral vasoconstriction and bradycardia[18 23] is initiated reflexly by stimulation of the ophthalmic division of the trigeminal nerve on immersion of the face in cold water. It plays a powerful role in oxygen conservation in diving animals, enabling some to remain submerged for periods in excess of 30 min. The response is enhanced by both anxiety and cold water. The magnitude of the diving response found in humans is qualitatively similar to that found in diving mammals, but quantitatively less marked, with the cold-shock response predominating in the majority of normally clothed adults.[92] Nevertheless about 15% of people do show a profound reaction[23] and this percentage increases with the use of specialist protective clothing, such as immersion "dry" suits,[92] which prevent rapid cooling of the cutaneous thermal receptors of the majority of the body, but leave those of the face exposed to the cold stimulus. Tipton, Kelleher and Golden[95] have reported that in such circumstances, where the cold-shock and diving responses are stimulated in roughly equal proportions, the resulting fluctuation in the competing parasympathetic and sympathetic chronotropic influences to the heart frequently (in 31 of 36 immersions) caused a variety of cardiac arrhythmias (predominantly supraventricular) just after the cessation of breath-holding in cold water.

The diving response is also reported to be more marked in infants than adults.[18] Gooden, in his excellent review,[33] argued that while the diving response alone is unlikely to explain the reported survival of those cases of protracted submersion in cold water, it does play a contributory role together with hypothermia. He hypothesized that survival from prolonged near-drowning appears to depend on a specific interplay between the diving response and hypothermia, resulting in a protective state of "hypometabolism". Peripheral vasoconstriction, associated with both the diving response and cold, depresses tissue metabolism and thus reduces body oxygen requirements. Gooden postulated that immediately on face immersion the diving response apnoea prevents water aspiration into the lungs. Even if water does enter the larynx he postulated that reflex glottal spasm prevents further penetration into the lungs. The associated bradycardia and selective redistribution of blood conserves oxygen stores thereby protecting the brain from hypoxia during the initial minutes of immersion. Gradually, with surface cooling, hypothermia develops so that by the time oxygen stores are depleted, cerebral metabolism has been reduced to a level which confers some protection from hypoxia.

While to some extent this hypothesis is plausible there are several questions that remain to be answered. First, why is it that in most cases of prolonged submersion who survived, sufficient water was aspirated to cause near-drowning? It is possible that aspiration, when it did occur, was a relatively terminal event when the diving response, or laryngospasm, could no longer be maintained because of profound hypoxia. However, from our understanding of surface cooling, discussed above, it is probable that profound hypoxia is present before significant brain cooling has occurred in this circumstance. Second, does the cold-shock response override the diving response in children as it does in adults?[41 92] The only evidence in the literature relating to children in this context is that of Ramey, Ramey and Hayward[80] who found that children could not hold their breath long enough for a diving response to occur; in their experiment however, the temperature of the water was 29 °C, above that normally associated with the initiation of the most powerful diving response. Skin temperature of children already playing in water is at or in the region of the water temperature and thus, if they become accidentally submerged, should not exhibit a cold-shock response. However, those children who fall into water without prior wetting should display a cold-shock response. Finally, another factor mitigating against the "hypometabolism" hypothesis is the large discrepancy in the rates of cooling reported (varying from 10 °C in 10 min in ice water[75 102] to 3.5 °C in 6 min in a young adult[85]). Such rates of cooling are not compatible with either surface cooling alone or in combination with a diving response.

Thus while not ruling out entirely the participation of the diving response in the early stages of some of these remarkable survival stories, it is considered that the rapid rates of cerebral cooling encountered may be largely dependent on pulmonary heat exchange after aspiration.

PULMONARY AND GASTRIC COOLING

After submersion, the victim may attempt to breath-hold for as long as possible before neurogenic afferents from the respiratory muscles or cutaneous thermoreceptors build to an intolerable level, forcing the individual to take a breath.[101] It has been shown that voluntary breath-holding can be extended by movements of the respiratory muscles, and swallowing, against a closed glottis.[101] This may be the explanation for the large amounts of water reported to have been found in the stomach of some drowning victims[11 27 67 78] but not in others[33] (i.e. ingestion of water is only likely to be found in those who attempted to extend voluntary breath-holding). Depending on the volume and temperature of the water swallowed, heat exchange between the blood and gastric wall could contribute significantly to blood cooling, especially in children. When continued breath-holding is impossible, aspiration of water into the airways and alveoli occurs with inspiration and possibly reflex coughing, provided reflex laryngeal spasm does not supervene.

Regardless of the method of entry of cold water into the "core" of the body, be it lungs, stomach, or both, it precipitates a decrease in deep body temperature. The magnitude of this decrease is directly proportional to the volume of water aspirated, its temperature differential with the body and state of the circulation. However, to protect the brain from hypoxic damage it would be necessary to cool the brain very rapidly, at least 7 °C in 10 min. This doubles cerebral hypoxia survival time[46] but even colder brain temperatures are required for longer survival periods.

Gooden[33] argues that, to explain some of the remarkable survival stories reported, such a mechanism of cooling lacks quantitative evidence. On simple thermal physical principles of "methods of mixtures", he points out that "a (normal) person would need to ingest an amount of ice-cold water equivalent to 20% of body mass in order to reduce the average body temperature to 30 °C. Thus a child weighing 20 kg would need to ingest approximately 4 litre of ice-cold water". Such volumes of aspirated water are not compatible with resuscitation[68] nor are they usually encountered in near-drowning victims.[36] Harries[37] stated that it is unusual to aspirate more than 200 ml but it is unclear how this estimation has been determined, particularly as it has been shown experimentally[69] that aspirated fresh water is quickly absorbed and redistributed within the body.

Gooden's calculation, however, appears to be based on the requirement for the entire body mass to be cooled to 30 °C. Using the same simple methods of mixtures, the volume of ice water necessary to cool the blood volume of a 20-kg child (approximately 1.6 litre) to 30 °C would be approximately 300 ml. It is accepted that this is a gross over simplification as the actual amount required to be aspirated to cool the brain would need to be in excess of this because of the dynamic heat exchange that would occur with the perivascular tissues and perfused organs; in addition, pulmonary heat exchange is reduced because of pulmonary shunting. Nevertheless, given that a large proportion of the cardiac output in a child in such circumstances (i.e. with generalized peripheral vasoconstriction) is diverted to the cerebral circulation, it is conceivable that selective cooling of the brain occurs some time before the general body mass equilibrates. Thus aspiration of cold water may play a critical role in the production of cerebral hypothermia and brain survival in the submerged child or young adult of relatively small body mass.

At first sight the volume of water required to be aspirated would appear to be in conflict with Modell's conclusion that volumes in excess of 22 ml kg^{-1} are usually incompatible with life. This would allow a maximum aspiration of 440 ml for a child with a body mass of 20 kg. While this is more than the theoretical 300 ml to cool the blood, as stated above, larger volumes would in reality be required to negate dynamic heat exchange with the perivascular tissues and perfused organs. However, during the drowning process, aspiration of water is unlikely to occur in one single bolus but is more likely to be a dynamic process with flushing of small volumes of cold water in and out of the lung. Fainer, Martin and Ivy[26] demonstrated in dogs that rapid violent respiratory movement continued for about 70 s after submersion. It is proposed that with each tidal volume of water aspirated, heat is exchanged but the total volume retained in the lungs when respiration ceases is significantly less than the total volume of water which has entered and exited the lungs up to that time.

This hypothesis is supported by a recent animal experiment by Conn and colleagues[16] which showed that aspiration of cold water produces extremely rapid blood cooling; in lightly anaesthetized dogs, the mean carotid artery temperature decreased by approximately 8.0 °C in the first 2 min of drowning, but only by 0.8 °C in a control head-out group of similarly shaved dogs; rectal temperature lagged "considerably behind". Regrettably the experimental method did not make it possible to estimate how much fluid had been aspirated in those 2 min. When the animals were killed after 10 min of submersion, the volumes aspirated, estimated from post-mortem weight changes, were considerably in excess of the accepted lethal level of 22 ml kg^{-1}.[68] Incidentally, it is quite difficult to find the origin of the value of 22 ml kg^{-1} quoted frequently by Modell and others; in the original report by Modell and Moya,[69] the value appears to be 20 ml lb^{-1}, with death caused by VF rather than irreversible pulmonary damage.

The theory of water flushing in and out of the lung rather than absorption of water as the primary cause of the rapid cooling of blood on submersion is supported further by data from Conn and colleagues.[16] The marked decrease in carotid artery blood temperature in dogs (average weight 9.2 kg) was 8.5 °C after 2 min in fresh water at 4 °C and 7.5 °C in salt water; while over the remaining 8 min of the experiment, mean carotid temperature decreased by another 2.4–10.9 °C in fresh water and by 3.1–10.6 °C in salt water. Body mass increased by 1.5 kg (fresh) and 0.6 kg (salt) in the 10 min. Although Conn and colleagues[16] reported that all animals were tachypnoeic on immersion, the study did not state when respiration ceased. In an earlier experiment by Fainer, Martin and Ivy,[26] using 160 dogs, it was reported that violent respiratory movement lasted approximately 71 s and thereafter respiratory movement was limited to the occasional agonal movement. Thus it would be fair to assume that, in the experiment by Conn and colleagues,[16] most of the aspiration had taken place during the 2-min period showing the greatest decrease in carotid temperature. Furthermore, if one assumes no, or little, absorption in the salt water group in this time, it suggests that in the equivalent fresh water group, 7.5 °C of the 8.5 °C decrease in blood temperature in the initial 2 min was caused by flushing and 1.0 °C by absorption of approximately 900 ml of fresh water.

AMBIENT COOLING

Increasingly, hypothermia has been recognized as a favourable prognostic indicator. However, the rate of onset of hypothermia is clearly critical; to be of benefit it must occur rapidly before profound hypoxia develops.

Exposure to cold ambient conditions during resuscitative procedures, while awaiting the arrival of the ambulance, facilitates continued cooling if adequate insulation is not provided. Furthermore, thermoregulation in the hypoxic individual is likely to be severely compromised. This, combined with high evaporate heat loss from wet clothing and increased conductive heat loss to the ground beneath the supine patient, cause deep body temperature to continue to decrease. By the time the victim arrives at hospital, body temperature, in a patient with intact circulation, may have decreased significantly. Unless such a decrease occurs quickly, and before hypoxia becomes severe, little useful cerebral protection is provided.

Thus cooling which occurs during rescue and transport to hospital is of little benefit and may render deep body temperature on arrival in hospital an unreliable prognostic indicator.

Rescue and treatment

RESCUE

Advice on rescue lies more correctly with rescue organizations but a few important principles are offered for consideration:

At all times it is important to ensure the safety of the rescuer in addition to the casualty.

- Landing a casualty should never be delayed to enable attempts at in-water resuscitation.
- Where possible, casualties wearing life jackets whose airway is clear of the water should be recovered in a horizontal attitude.[32]

- The possibility of cervical spine trauma should be considered in unconscious victims rescued from shallow water and appropriate measures and techniques used.[37]

TREATMENT

Out-of-hospital management

It should be presumed that all near-drowning victims rescued from UK open waters are hypoxic, acidotic and hypothermic.

The primary aims of treatment of the near-drowned are listed below in order of priority:

- Effective immediate relief of hypoxia. The speed of achieving this has the greatest influence on outcome.[73,87]
- Restoration of cardiovascular stability.[87]
- Prevention of further heat loss.
- Speedy evacuation to hospital.

Airway patency and adequate ventilation should be achieved rapidly. There is a significant risk of regurgitation and aspiration of gastric contents during resuscitation.[74] Tracheal intubation, if indicated, should be carried out at the earliest opportunity.[87] High fractional inspired oxygen ($F\mathrm{IO}_2$) should be delivered using a self-inflating bag and reservoir; if available, a positive end-expiratory pressure (PEEP) valve set to 5 cm H_2O should also be used. Application of cricoid pressure during EAR, or bag and mask ventilation, reduce the risk of regurgitation and aspiration.[74]

The use of the Heimlich manoeuvre in near-drowning has been considered by the Emergency Cardiac Care Committee of the American Heart Association and is not recommended.[83] There is insufficient evidence to support the claims that it is effective in removing aspirated liquid. Additionally, the manoeuvre itself may delay early intubation, aggravate visceral or spinal injury, cause confusion among rescuers with yet another procedure to follow,[83] induce vomiting[74] and increase the risk of precipitating an undesirable cardiac arrhythmia in the hypothermic casualty rescued from cold water.

In the hypothermic near-drowning casualty, because of the marked cold-induced peripheral vasoconstriction, characteristically low volume and profound bradycardia, peripheral pulses are notoriously difficult to feel. Accordingly, the carotid artery should be palpated gently for at least 1 min.[37,74] Extreme caution must be taken not to precipitate VF by rough handling.[75] VF responds poorly to defibrillation at core temperatures less than 28 °C; at this temperature, Purkinje tissue looses its conduction advantage over normal ventricular muscle fibres. Nevertheless, it may be worth attempting, especially in children, as some successes have been reported.[88,100] However, even when sinus rhythm is achieved at these temperatures it tends to be unstable and revert easily to VF. If attempts at defibrillation at less than 28 °C are not immediately successful they should be discontinued until cardiac temperature increases to greater than 29 °C.

The casualty should be insulated against further heat loss and transported to the nearest emergency department as rapidly as gentle handling allows.[88] Any life-support measures instituted at the scene should be continued during transportation.[74] Some authors advocate immediate transfer of all severely hypothermic and clinically lifeless patients to the nearest facility with cardiopulmonary bypass facilities.[11,60]

Hospital management

Near-drowning is an emergency: even those victims who appear normal on arrival at hospital can deteriorate rapidly.[74] An accurate, rapid initial assessment of the victim is essential. A suggested algorithm for subsequent management, based on the classification by Simcock of near-drowning victims,[87] is shown in figure 1.

Survival figures for victims of near-drowning are very encouraging for those with a minimal reduction in the Glasgow coma score (GCS) but much less favourable for those with low scores.[34,74] Factors

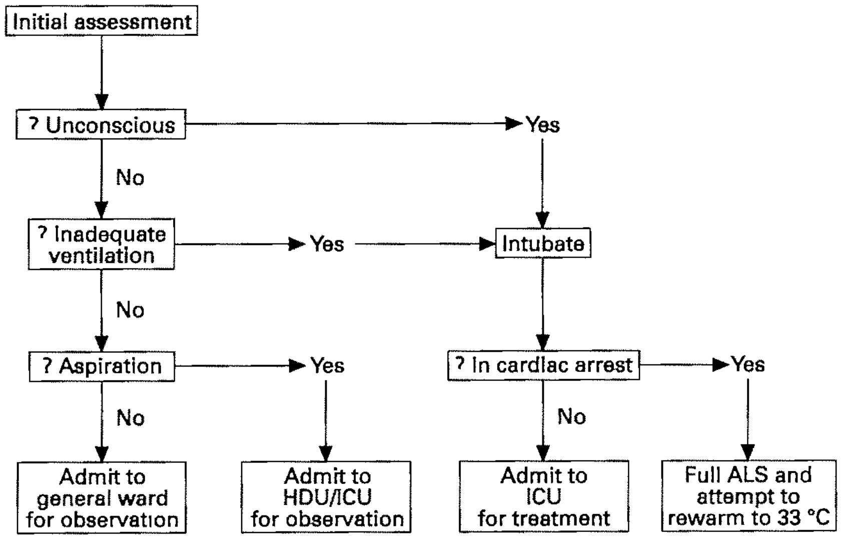
Initial assessment
? Unconscious
Yes
No
? Inadequate ventilation
Yes
Intubate
No
? Aspiration
Yes
? In cardiac arrest
Yes
No
No
Admit to general ward for observation
Admit to HDU/ICU for observation
Admit to ICU for treatment
Full ALS and attempt to rewarm to 33 °C

Figure 1 A suggested algorithm for management of near-drowning, based on the classification by Simcock of near-drowning victims.[87] ALS=Advanced life support.

Table 1 Favourable prognostic indictors for near-drowning

- Children 3 yr+[9 73]
- Female[34]
- Water temperature <10 °C[11]
- Duration of submersion <5 min[73], <10 min[9]
- No aspiration[9]
- Time to effective basic life support <10 min[73]
- Rapid return of spontaneous cardiac output
- Spontaneous cardiac output on arrival in emergency department[10 69]
- Core temperature <35 °C[9], <33 °C[10]
- Minimum blood pH >7.1[73]
- Blood glucose <11.2 mmol litre^{-1}[6 34]
- GCS. no coma on admission[34 69 73]. GCS >6[19]
- Pupillary responses: present[34 69]

which have been associated with favourable outcome are listed in table 1, but none, either individually or in combination, has been shown to have absolute predictive significance.[9] Therefore, full resuscitative efforts should be attempted in all near-drowning patients arriving in emergency departments.

Patients with no evidence of aspiration

Victims of near-drowning who appear normal in the emergency department can deteriorate unexpectedly. All should be admitted to a general ward for a period of observation, generally accepted to be a minimum of 6 h.[37] Other authors, however, consider it prudent to admit the victim for 24 h because of the risk of late onset pulmonary and cerebral oedema.[68 75 87] It is recommended that the investigations listed in table 2 are considered. Hypothermic patients who are conscious and cooperative can be rewarmed in a bath of warm water (40 °C) until rectal temperature has increased to 36 °C. Arterial blood-gas values, obtained while breathing air, and core temperature must be normal before discharge. Signs of aspiration, which may become manifest later, include cough, tachypnoea, retrosternal discomfort, audible crackles on auscultation of the chest, abnormal arterial oxygen tension with the patient breathing air, abnormal chest x-ray and fever.

Infection after immersion is common; usually this is confined to the chest, although there are reports of intracerebral abscess and septicaemia.[37] However, the benefits of prophylactic antibiotic therapy have been questioned.[74] It is generally agreed that antibiotic therapy should be withheld until bacteriological studies, or clinical examination, indicate active infection.[68] Patients should be informed of the potential seriousness of any pyrexial illness which develops within a few days of discharge. They should be advised to attend either their general practitioner or return to the A&E department in such an event.

Table 2 Suggested investigations for near-drowning patients

- Arterial blood gas analysis
- Biochemistry:
  - Electrolytes
  - Glucose
  - Urea and creatinine
  - Total creatinine kinase
- Coagulation studies
- Haematology
- Blood and tracheal aspirate for aerobic and anaerobic culture
- Chest radiograph
- Electrocardiogram
- Rectal temperature measured at least 15 cm from the anal sphincter
- Drugs screen for overdose of:
  - Alcohol
  - Tricyclics
  - Benzodiazepines
  - Paracetamol
  - Aspirin, etc

Patients with evidence of aspiration but without ventilatory compromise

These patients may develop pulmonary oedema and deteriorate precipitously. Accordingly, they should be admitted to a high dependency (HDU) or intensive care unit (ICU). Monitoring should include continuous pulse oximetry and frequent arterial blood-gas analysis. The onset of pulmonary oedema is usually within a few hours of aspiration of water, either fresh or salt, and can be rapidly progressive. Continuous positive airways pressure (CPAP) support provided by a mask or nasal cannula (in infants who are obligate nasal breathers),[74] should be offered in the first instance. The aim is to achieve an arterial oxygen partial pressure (Pa_{O_2}) of more than 8 kPa with an FI_{O_2} less than 0.5. If this is unsuccessful the facility for tracheal intubation and intermittent positive pressure ventilation (IPPV) with PEEP must be available immediately.

Patients with ventilatory compromise or hypothermia, or both

Patients who have clinical or investigative evidence of inadequate ventilation must undergo tracheal intubation and ventilatory support with PEEP.[68] This should be maintained at 8–10 kPa or at 10–12 kPa in those with ischaemic heart disease. Ideally, FI_{O_2} should be less than 0.5 and PEEP provided at the lowest pressure consistent with minimizing intrapulmonary shunt and achieving these aims.[74 87]

All victims of near-drowning who are hypothermic should be rewarmed in an ICU with continuous monitoring.[75] Those who are cardiovascularly stable may be warmed slowly but actively, at a controlled rate of approximately 1 °C h^{-1}. This can be achieved using warmed humidified inspired gas, warmed i.v. fluids, warming mattress/blanket or wrapping exposed areas in dry woollen blankets. It is advisable to consider rapid rewarming for any patient whose core temperature is less than 28 °C because of the perilous state of the myocardium and its propensity for ventricular arrhythmias below this temperature. Patients who have an unstable cardiovascular system or are in cardiopulmonary arrest should be warmed more aggressively with consideration given to extracorporeal rewarming (ECR) using haemofiltration or cardiopulmonary bypass (CPB).[47 98]

Methods used to rewarm rapidly without ECR include bladder irrigation, gastric lavage,[85] oesophageal heat interchanger,[57] pericardial lavage, peritoneal dialysis,[85] thoracotomy and pleural lavage.[50] The easiest way to accomplish this in most hospitals is peritoneal dialysis.[85] The dialysate

(2 litre of potassium free) is warmed to 54 °C so that it enters the peritoneal cavity at 43.5 °C, and hourly cycles are preferred.[85]

The advantages of ECR are rapid restoration of normothermia up to 10.7 °C h^{-1},[98] reduction of high blood viscosity found in hypothermia and, most importantly, when bypass is used, there is reinstitution of perfusion regardless of cardiac rhythm[11] with avoidance of "rewarming shock". An additional benefit is the ability to rapidly off-load ultrafiltrate in the presence of overwhelming pulmonary oedema; Norberg and colleagues removed 2300 ml in 1 h to facilitate withdrawal from CPB.[72]

Those in cardiopulmonary arrest

Full resuscitation must be attempted in accordance with the Resuscitation Council (UK) guidelines and an attempt made to rewarm the casualty to 33 °C. This may cause manpower problems when prolonged external chest compressions (ECC) are required. Successful manual massage maintained for a period of 4.5 h has been demonstrated,[90] while Ireland and colleagues reported success after 5.5 h using a "Thumper" cardiopulmonary resuscitator system (Michigan Instruments Inc., Grand Rapids, MI, USA) mechanical device.[47] The advantage of a mechanical device is to ensure consistent effective compression during rewarming thus maintaining an adequate circulation to meet metabolic demands and facilitate regular emptying of the heart during ECR.[47] Jones and Swan also recommend the use of such devices in prolonged resuscitation.[49]

Cardiopulmonary bypass

Rewarming by institution of emergency CPB has been used with dramatic effect in severely hypothermic casualties who were in full arrest,[11 43 47 49 98] many after submersion in cold water.[50 60 72 99] The most notable of these was the neurologically intact survival of a 2.5-yr-old girl who was trapped under ice for 66 min.[11]

The majority of reports describe partial bypass from the femoral artery to femoral vein.[11 43 49 98] Norberg and colleagues described conversion to full bypass to achieve faster flow rates and decompression of a dilating asystolic heart in a 7-yr-old boy with a successful outcome.[72] Letsou and co-workers suggested that full bypass using median sternotomy is the method of choice.[60] There is also a report of successful resuscitation in one of two hypothermic adult casualties using a modified dilatational/Seldinger technique to apply percutaneous CPB via the femoral veins, with a portable pump and paediatric oxygenator.[79] CPB provides fast rewarming of the core, maintains tissue perfusion and oxygenation while assisting the cold and inefficient heart to regain normal electromechanical function.

The advocates of median sternotomy claim that exposure and cannulation of the aorta and right atrium is faster than dissection and cannulation of the femoral vessels in the pulseless patient, and that flow rates are faster. There may also be advantage in having access to the heart for massage, defibrillation and decompressive venting of a cold and dilating ventricle.[60] A survey of members of the American Association of Thoracic Surgeons and the Southern Thoracic Surgical Association in the early 1980s produced evidence of 174 cases of hypothermia rewarmed with CPB with a survival rate of 45%.[60] A review of the literature in 1994[97] analysed data from 68 hypothermic patients undergoing CPB. In reports describing attempted resuscitation of two or more cases the survival rate was 50%; if case reports and singletons were included the rate improved to 60%. VF was associated with greater survival than asystole, but the difference (73% *vs* 52%) was not significant. Walpoth and colleagues also noted that documented VF had a favourable outcome with CPB in hypothermia.[98] Eighty percent of survivors returned to their previous level of function. The recommendations of that review were that CPB resuscitation is advised for hypothermic patients in arrest and for those with core temperatures less than 25 °C, irrespective of rhythm; patients in a stable rhythm of 25–28 °C can be treated with CPB or conventional warming methods.[97] The maxim "nobody is dead until warm and dead" should always be borne in mind.[35]

Cessation of resuscitative efforts

Hyperkalaemia in severely hypothermic patients is usually indicative of asphyxial cardiac arrest before significant cooling occurred.[63] A potassium concentration in excess of 10 mmol $litre^{-1}$ is not compatible with successful resuscitation[39 84] and is advocated for use in the triage of avalanche victims.[12]

Hypoxic encephalopathy is probably the most debilitating of the consequences of near-drowning. The majority of flaccid, comatose victims admitted to the ICU suffer either severe cerebral injury or cerebral death. Early prediction of outcome requires accurate determination of the nature and extent of neurological injury; it is also fundamental for patient management. In children, there are four distinct outcomes: full recovery, neurologically impaired survival, persistent vegetative state and death.[8] Cerebral resuscitative efforts to reverse the changes of hypoxic damage and reperfusion injury have rarely been successful.[66 74] Poor outcomes are especially likely when ICP >20 and CPP <60 mm Hg, despite therapy.[74]

Prognosis

One USA source[14] cited by Orlowski[75] estimated that one-third of all near-drowning survivors were moderately to severely brain damaged. The prognosis for children in the UK appears to be similar: of 188 hospital resuscitations of near-drowning patients reported by Kemp and Sibert,[53] 33 had fixed dilated pupils on admission to hospital; of these 13 died, 10 had severe residual neurological defects (spastic quadriplegia) and 10 recovered fully. A recent report from Seattle[34] found an unfavourable outcome in patients who were comatose on admission: of 72 admissions there were 38 deaths, 14 in a vegetative state, three with dependent neurological impairment, six with mild neurological impairment and 11 discharged normal. The Australian experience was similar: 31 admissions with cardiac arrest of whom 17 died and six survived with severe spastic quadriplegia.[100] This could be related to the warmer waters found in the Brisbane area. This view is supported by the Canadian experience[10] where prolonged in-hospital resuscitation and aggressive treatment of near-drowning victims who initially had absent vital signs and were not hypothermic (>33 °C), resulted either in eventual death or an increase in the number of survivors with a persistent vegetative state.

A prognosis score for paediatric near-drowning victims has been derived by Orlowski.[74] It is based on five indicators: age younger than 3 yr, maximum submersion estimated longer than 5 min, post-rescue delay in resuscitation for greater than 10 min, coma at time of admission to hospital and initial pH less than or equal to 7.1.

Neurological classification of 101 paediatric drowning and near-drowning victims based on the level of consciousness, as assessed by GCS, has been used for prognostic purposes.[19] GCS<5 predicted a high-risk group of patients with 80% mortality or permanent neurological sequelae. In general, 2–6 h after the accident, patients who remain decorticate, decerebrate or flaccid fair poorly; patients who are improving at this time, but remain unresponsive, have a 50% chance of doing well, while those who are showing definite signs of improvement (alert, stuporous or obtunded but responding to painful stimuli) generally do well and most have a normal or near normal outcome.[74] A recent article by Kreis and colleagues[56] suggested that the most accurate method of predicting neurological outcome is by magnetic resonance spectroscopy (MRS): their spectroscopic prognosis index distinguished between good (n=5) and poor (n=11) outcome, with one false negative after a borderline MRS result, and no false positive results (100% specificity).

It is generally agreed that hypothermia is neurologically protective, especially in children, although Kruus and co-workers concluded that a core temperature of less than 30 °C is indicative of prolonged immersion and therefore of more severe brain hypoxia.[58] In reports where rapid reversal of the hypoxic state was achieved, in combination with ICU support, often with ECR and occasionally with control of intracranial pressure (ICP), there was complete or near-complete return of neurological function with time.[11 85 86 102]

Many studies assessing predictive factors have analysed data from near-drownings in warmer waters than are usually found in the UK.[19] Therefore, it may be inappropriate to assess immersion victims using the same criteria, as the presence of hypothermia may offer some cerebral protection.[10]

Complications

In addition to the complications already described (pulmonary oedema, infection, hypothermic cardiac arrhythmia, hypoxic encephalopathy and cerebral oedema), disseminated intravascular coagulation (DIC) has been described in near-drowning,[85] as has rhabdomyolysis.

Rhabdomyolysis complicated by acute renal failure has been reported in two normothermic casualties of near-drowning in cold (14 °C and 17 °C) surf.[2] One victim who was retrieved in cardiopulmonary arrest and was alert, lucid and apparently normal 1 h later, had a plasma creatinine concentration of 2106 μmol litre^{-1} 3 h after immersion. He required support with peritoneal dialysis for 11 days and forced saline diuresis to avert oliguria. The second patient discharged 2 h after the event, re-presented 24 h later complaining of weakness, myalgia and dark urine. His serum creatinine concentration was 359 μmol litre^{-1}, and forced saline/frusemide diuresis avoided the need for dialysis. Excessive or sustained muscle exercise and heat stress are well recognized causes of rhabdomyolysis; cold stress is a significantly less common trigger. However, in view of the potential consequence of acute renal failure, it would seem prudent to measure total creatinine kinase activity in addition to serum electrolytes and simple urinalysis in survivors of near-drowning.

Peripheral neurological sequelae may be manifestations of traumatic or even "non-freezing cold injury" to peripheral nerves rather than hypoxic damage from near-drowning. One should also be mindful of the near-drowning patient having a predisposing injury or medical condition, while the possibility of there being a drug-related condition should also be borne in mind.

Other treatment modalities

Artificial surfactant (Exosurf) has been used successfully in the management of a 9-yr-old victim of near-drowning with a rectal temperature of 30.3 °C who was acidotic (pH 6.95).[62] Despite circulatory and ventilatory support ($F\text{I}_{O_2}$ 1, minute volume 230 ml kg^{-1}, PEEP 5 cm H_2O, peak ventilator airway pressure 40 cm H_2O) acidosis persisted and there was severe and progressive respiratory distress (pH 6.87, Pa_{O_2} 7.6 kPa, Pa_{CO_2} 12.4 kPa, base excess −17.5 mmol litre^{-1}). Four hours after admission artificial surfactant was instilled slowly via the tracheal tube. Within 5 min there was an improvement in gas exchange (Pa_{O_2} 11.5 kPa, Pa_{CO_2} 9.5 kPa) and a decrease in peak pressure to 30 cm H_2O, with no change in ventilator settings. His trachea was extubated 3 days later and he was discharged neurologically intact.

Animal models of near-drowning have failed to demonstrate any improvement in pulmonary function after the use of exogenous surfactant,[47 76] although damage to the alveolar capillary membranes is reduced. This disappointing finding may be a result of using volumes of surfactant which were too large and instilled too soon after injury, causing documented severe hypoxia (i.e. a second major insult). The use of smaller volumes, instilled or nebulized at different times, with additional PEEP, have not been reported.

A study on the effect of corticosteroid therapy on survival and blood-gas exchange in dogs after aspiration of fresh water drowning demonstrated no beneficial effect.[13] Their value in the management of pulmonary injury has not been proved[68] and probably should not be used.[74]

Conclusions

The rapid onset of cerebral hypothermia would appear to be the essential mechanism by which some submerged victims, in particular children, appear to be able to withstand protracted periods of asphyxia without suffering irreversible neurological damage. For this protective mechanism to be effective, brain cooling must be established rapidly, before severe hypoxia occurs. Such rates of cooling are unlikely to be achieved through surface cooling alone, or in combination with the diving reflex. It is postulated that rapid selective brain cooling is achieved through pulmonary heat exchange by repeated flushing of the lungs with cold water during the drowning process before cardiorespiratory arrest supervenes.

Successful treatment depends on speedy recovery and the immediate institution of CPR if indicated. All near-drowning victims, even those who appear to be ostensibly clinically well, should be transferred to hospital for pulmonary screening. Although some successful resuscitations of victims in cardiac arrest who are flaccid with fixed dilated pupils have been reported, the great majority would appear to have a poor prognosis. The prognosis is better for those with profound hypothermia but rewarming may be difficult in the absence of a good circulation. Accordingly, consideration should be given to transferring all profoundly hypothermic patients who are in cardiac arrest to a centre where cardiopulmonary bypass facilities are available, sooner rather than later.

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Aspects of resuscitation in trauma

J. P. NOLAN AND M. J. A. PARR

In 1988, the Royal College of Surgeons Working Party Report on the management of patients with major injuries[112] highlighted serious deficiencies in the way trauma patients were managed in the UK.[5] At the end of the same year, in an attempt to improve evaluation of UK trauma services, several hospitals started to contribute data to the Major Trauma Outcome Study (MTOS (UK)).[148] This audit system had been established in the USA by Champion and colleagues in 1982.[26] The first report from MTOS (UK), published in 1992, was based on 2 yr of data from 33 hospitals.[157] Unfortunately, its conclusions echoed those of the Royal College of Surgeons' report 4 yr earlier: "the initial management of major trauma in the United Kingdom remains unsatisfactory". Specifically, the mortality for 6111 patients sustaining blunt trauma and treated in the 14 busiest hospitals was significantly higher than that predicted from a comparable US data set (actual 408 *vs* predicted 295.6; $P<0.001$). Other key findings from this report were: (a) 21% of patients with an injury severity score (ISS) greater than 15 took longer than 1 h to reach hospital, and (b) a senior house officer was in charge of initial hospital resuscitation in 57% of seriously injured patients.

What initiatives have been taken in an attempt to correct these deficiencies in trauma patient management? Has the outcome for seriously injured patients in the UK been improved? This review addresses these questions while covering the following topics: pre-hospital trauma resuscitation, communication, advanced trauma life support (ATLS), trauma teams, airway management, fluid therapy and resuscitation end-points.

Pre-hospital trauma resuscitation

Apart from the severity of injury, probably the single most important factor determining the outcome of a trauma patient is the time interval from the moment the injuries are received to the provision of definitive care. Definitive care for the trauma patient implies achieving a clear airway and effective ventilation, haemorrhage control and restoration of an adequate blood volume.

A recent retrospective study of pre-hospital trauma deaths in North Staffordshire reported that, on the basis of post-mortem evidence, airway obstruction had been present in two-thirds of those patients in whom death was judged not to have been inevitable.[63] Although one can criticize the design of this study, there is a clear message: more bystanders must be trained in simple first-aid and the interval between the time of injury and arrival of the emergency services must be reduced. The authors of this study suggested that first-aid could be tested at the time of the driving test. Current standards for ambulance response times dictate that 50% of all calls are responded to within 8 min and 95% within 14 min (urban areas) and 19 min (rural areas). The ambulance performance standards have been reviewed recently and in the future some form of prioritized dispatch system will be used in an attempt to achieve the new government targets (table 1).[24]

The main controversies in pre-hospital trauma management concern the type of pre-hospital provider and the interventions they perform. In common with the emergency medical services (EMS) in the USA, most of the UK uses a

Table 1 Proposal for prioritized ambulance response times. **An interim target of 75% within 8 min has been accepted for implementation in England from 2000–2001.

Immediately life threatening (category A*)	90%<8 min**
Serious (category B)	50%<8 min 95%<14 min
Not life-threatening or serious	Local decision

*Patients in category A are:

A1. Adults with chest pain associated with any of the following: pallor, cyanosis, shortness of breath, sweating, nausea or vomiting; but specifically excluding those for whom the pain is intensified by breathing.
A2. Individuals who are unconscious, fitting or unresponsive for any cause.
A3. Individuals with severe breathing problems who are unable to speak whole sentences.
A4. Injuries to the head or trunk.
A5. Individuals recognized as having anaphylactic shock.
A6. A woman with severe obstetric haemorrhage.
A7. A child under the age of 2 yr.

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JERRY P. NOLAN, FRCA, Royal United Hospital, Combe Park, Bath BA1 3NG. MICHAEL J. A. PARR, MRCP, FRCA, Frenchay Hospital, Bristol BS16 1LE.

paramedic-based system. In other parts of Europe (in particular, France, Germany and Belgium) ambulance technicians are supported by physicians, usually anaesthetists, in mobile intensive care units (MICU). In the UK, ambulance technicians are trained in basic airway management, cervical spine control and shock advisory defibrillation. Paramedics have the additional skills of tracheal intubation, i.v. cannulation, fluid therapy and use of i.v. analgesia.[125] Supplementary skills provided by physicians include: use of neuromuscular blocking drugs and a broader range of analgesia and fluids, insertion of chest drains, cricothyroidotomy and the ability to triage the patient to the most appropriate hospital. In theory, the physician's ability to provide a more sophisticated and individualized continuum of patient care (not necessarily protocol-driven) in the initial hospital phase may expedite definitive care. Unfortunately, there are no randomized, controlled studies proving that the outcome for trauma patients is influenced by the type of pre-hospital provider or even the procedures performed. There are only small, retrospective, observational studies which have produced conflicting results.[73, 10[illegible], 115, 116, 121, 126] Some studies have suggested that ALS procedures improve physiological variables but not outcome.[25] One of the problems with pre-hospital trauma studies is the lack of a uniform system or set of definitions for reporting results. A working group has been convened to develop "Guidelines for uniform recording and reporting of performance and outcome after trauma" very much along the lines of the Utstein template for the reporting of pre-hospital cardiac arrest.[134] It is hoped that this will enhance the ability to compare data derived from different EMS systems.

A prominent American emergency physician stated recently that "despite our beliefs and biases, EMS is enormously over-funded in relation to our current ability to scientifically justify its effectiveness".[128] This dearth of quality data fuels the "scoop and run" *vs* "treat in the street" debate. To address this problem in the UK, the NHS Executive have commissioned the Medical Care Research Unit at the University of Sheffield to carry out an evaluation of the use of paramedic skills in pre-hospital trauma care.[62] This study involves three ambulance services and compares treatment by ambulance personnel with basic life support (BLS) skills only with first response by BLS crew with an ALS crew attending when requested, with immediate attendance by an ALS ambulance crew. The study is in part a retrospective, observational study, and in part a prospective, randomized study. It will assess the cost-effectiveness of ALS skills and their influence on various outcome measures. The results of this study will be presented later this year (S. Hughes, personal communication). In the meantime, except where patients are trapped, it would seem logical to limit interventions at the scene to establishing an open airway and effective ventilation, controlling external haemorrhage with pressure and expediting transport to a trauma centre. For penetrating cardiac injuries, delays of just 15 min in transportation increase morbidity and mortality, and rapid transport with BLS may give the best chance of survival.[47]

PRE-HOSPITAL ADVANCED AIRWAY MANAGEMENT

Airway management of the trauma patient in the pre-hospital setting is fraught with difficulties. As yet, there is no perfect method. The ideal would be a simple technique that provided effective ventilation, with little risk of gastric insufflation, and which did not have adverse cardiovascular effects in hypovolaemic or head-injured patients. While tracheal intubation remains the gold standard for airway management, it is often an unrealistic expectation in the pre-hospital setting. Pre-hospital personnel must be taught the technique and perform it frequently enough to maintain the skill. They are not able to use neuromuscular blocking drugs, access to the patient may be difficult and being able to see the larynx in strong sunlight can be almost impossible. To compound the problem, the popularity of the laryngeal mask among anaesthetists is limiting the opportunity for paramedics to learn and practice intubation. Are there satisfactory alternatives?

Bag–valve–mask

Bag–valve–mask ventilation with the use of oropharyngeal or nasopharyngeal airways is a difficult skill to master, is best performed by two individuals and has a high potential for gastric insufflation.[7]

Combitube

The Combitube is a double-lumen tube which is designed to ventilate the patient's lungs whether the tube enters the trachea or the oesophagus. It enters the oesophagus in approximately 90% of insertions. Massive inflation of the stomach occurs if ventilation is applied to the incorrect tube, so confirmation of correct placement is essential. The Combitube has been used successfully during cardiopulmonary arrest[43] and has been evaluated by paramedics in the pre-hospital setting[130] but is contraindicated in severe oropharyngeal trauma.

Laryngeal mask airway

The laryngeal mask airway (LMA) allows rapid, effective ventilation with a single operator, with improved oxygenation, less hand fatigue and probably less risk of gastric insufflation compared with bag–mask–valve ventilation.[19] Although the LMA does not completely protect the airway from aspiration, the risk of this has almost certainly been overstated. Furthermore, the significant risk of unrecognized endobronchial, or worse, oesophageal placement of a tracheal tube is often overlooked. From the perspective of ambulance service personnel, the LMA has several advantages compared with the tracheal tube. Training in use of the LMA is quicker and easier than for tracheal intubation[105] and the retention of skills with the

LMA is better; this would overcome some of the training difficulties faced by ambulance trusts.

The LMA protects the upper airway from soiling from above.[69] This is particularly relevant to the trauma patient with maxillofacial injuries in whom the risk of aspiration of blood is greater than the risk of aspiration of gastric contents. In a recent review of severe trauma patients, 15 patients had aspirated before arrival of an ambulance[85]; of these, 12 had aspirated blood, only two had aspirated blood and vomit, and one had aspirated vomit only.

The LMA may be inserted successfully where access to the patient is limited, for example in entrapments. The LMA can be inserted from the front of the patient while the head and neck are maintained in neutral alignment.[49] Insertion of the LMA causes less cardiovascular response[152] and increase in intracranial pressure (ICP) than laryngoscopy or tracheal intubation. Thus the LMA may offer some advantages for head-injured patients where the increase in ICP in response to laryngoscopy and tracheal intubation, and any coughing and straining, contributes to secondary brain injury. An observational study of pre-hospital use of the LMA has been reported from South Australia.[48] Thirty ambulance officers attempted 233 insertions in the field over a 12-month period and achieved 81% success rate. Sixteen of these were in trauma patients.

In the UK, it would seem logical for both ambulance technicians and paramedics to be trained to insert LMA. The LMA provides the technician with a more effective device than the simple Guedel airway, and gives the paramedic a backup should intubation prove impossible.

PRE-HOSPITAL SURGICAL AIRWAY

If a patient has an obstructed airway, and intubation or LMA insertion are not possible, cricothyroidotomy is a life-saving procedure. In many North American states paramedics are trained to perform cricothyroidotomy and apparently achieve this with considerable success. A recent study of 50 cricothyroidotomy attempts in trauma patients by paramedics in Indiana concluded that the procedure was successful in 47 (94%).[67] This is in close agreement with a study of the procedure performed by air ambulance flight nurses in which a surgical airway was established successfully in 68 of 69 patients (98.5%), with an acute complication rate of 8.7%.[18] As yet, paramedics in the UK are not trained to perform surgical airways. One of the main concerns expressed by ambulance service trainers is that the likelihood of any given paramedic having to perform the procedure would be very low, therefore, even if they could be trained they would have a limited opportunity to maintain the skill. Although this is undoubtedly true, the same argument must apply to most anaesthetists, yet we, quite rightly, are expected to perform a surgical airway in an emergency. Physicians on the London Helicopter Emergency Medical Service (HEMS) perform cricothyroidotomy if a secure, patent airway cannot be established by any other means.[156] HEMS doctors attend to particularly difficult (often trapped) trauma cases and are in a unique position to collect data on the pros and cons of pre-hospital cricothyroidotomy.

PRE-HOSPITAL I.V. FLUID MANAGEMENT

Should a severely injured patient be given i.v. fluids before arrival at hospital? This question is at the hub of the most controversial debate in pre-hospital trauma patient management. Many of the issues also apply to in-hospital fluid resuscitation. The two opposing views on fluid resuscitation are discussed in turn, followed by what we think is a rational solution!

Do not give pre-hospital i.v. fluid

Provided that pre-hospital times are short, some would argue that establishing venous access is not a priority, that the procedure is time consuming and that insignificant volumes of fluid are infused before arrival at hospital.[32,73,107,126] Furthermore, in the presence of uncontrolled bleeding, aggressive fluid therapy may be detrimental. On the basis of several animal studies of uncontrolled haemorrhage it was concluded that i.v. fluids increase arterial pressure but also reverse vasoconstriction, dislodge early thrombus, increase blood loss, cause a dilutional coagulopathy and reduce oxygen delivery causing a metabolic acidosis.[10,11,22,76,132] In these animal studies, allowing arterial pressure to stay low until control of haemorrhage was achieved, so-called permissive hypotension, improved survival. A close clinical analogy is the patient with a ruptured abdominal aortic aneurysm. In these cases it has been suggested that fluid resuscitation should be minimal in all but the moribund, and a systolic arterial pressure of 50–70 mm Hg should be maintained until the aorta is clamped.[28] The mortality rate of 23% quoted by protagonists of this approach contrasts markedly with a mortality rate of 70% in aneurysm patients who received vigorous fluid resuscitation before surgery.[68] The laboratory research was transplanted to the clinical trauma arena by Bickell and colleagues.[12] In a prospective, controlled study, patients with penetrating torso injury and a pre-hospital systolic arterial pressure of less than 90 mm Hg received either standard i.v. fluid therapy or underwent venous cannulation but received no fluid until arrival in the operating theatre. Of 289 patients receiving delayed fluid resuscitation, 203 (70%) survived to discharge from hospital, compared with 193 of 309 patients (62%) who received immediate fluid resuscitation (P=0.04). In a more recent analysis of these data, patients were sub-grouped into major vascular injury, solid organ injury, non-cardiac injury and cardiac injury. While there was a trend towards an improved outcome in all groups, the only patients in whom a statistically significant improvement in in-hospital mortality could be demonstrated were those with penetrating cardiac injury.[147a] This study has raised many methodological concerns and several traumatologists[23,124] disagree with the authors' conclusions.

Give pre-hospital i.v. fluid

The opposing view is that fluid resuscitation should be started immediately because the longer the period of hypotension, the greater the risk of complications and death, and that hypovolaemia is the cause of one-third of pre-hospital fatalities.[31] Most clinicians would agree that the conclusions of the study of Bickell and colleagues were obtained under very specific circumstances: all patients were injured within the city limits of Houston, only those with penetrating injuries to the torso were included, the mean age of patients was only 31 yr and pre-hospital times were extremely rapid (mean interval between call and arrival at the trauma centre was 30 min). Furthermore, the authors did not discuss the causes of death or details of airway intervention. It would be unwise to extrapolate the findings of this study to older patients with chronic illness, blunt trauma, those with head injuries or to other EMS systems where pre-hospital times may not be as short. There are problems extrapolating from laboratory animal studies to the human trauma victim. Although in porcine models gut barrier function remains intact and survival is good after prolonged hypotension with a mean arterial pressure of 40 mm Hg, the same may not apply to the trauma patient with complicated multiple pathology.[46 132 140]

There are at least two circumstances where minimal or no pre-hospital fluid resuscitation is likely to be extremely detrimental: patients with head injury and those where pre-hospital times are prolonged. In both of these situations there is little point in delivering the patient for definitive care when they have already received an overwhelming ischaemic insult. The patient will die regardless of the quality of in-hospital resuscitation. Hypoxia or hypotension increases dramatically the morbidity and mortality after severe head injury, and therefore oxygenation and an adequate cerebral perfusion pressure must be maintained at all times.[27 133 147] As cerebral perfusion pressure (CPP)=mean arterial pressure (MAP) − ICP, and assuming an ICP of 20 mm Hg in a patient with a severe head injury, MAP of at least 90 mm Hg needs to be maintained to provide a CPP greater than 70 mm Hg. Hypotension must be treated aggressively to prevent irreversible ischaemia.

Where the pre-hospital phase is prolonged, adequate perfusion of vital organs (especially gut and kidneys) reduces the risk of subsequent multiple organ failure. The gut is a silent organ in the resuscitation setting. Gut perfusion suffers early and may not return despite achieving apparently appropriate resuscitative goals (see resuscitation end-points, below).

A solution to pre-hospital fluid therapy

There is little doubt that the arrival of the trauma patient in the emergency department with venous access secured is an advantage. Attempts at pre-hospital venous cannulation are acceptable provided they do not delay the transfer of the patient to definitive care or distract from maintaining an open airway with effective ventilation and haemorrhage control. Cannulation en route does not add extra time and surprisingly may be as successful as when attempted at the scene.[66 100]

It is difficult to generalize but in most circumstances fluid resuscitation should be kept to the minimum required to maintain a viable outcome for vital organs until definitive control of haemorrhage has taken place. What is the minimum for any given patient and how can this be assessed in the difficult pre-hospital environment? Should we accept a relatively low arterial pressure. Sustained hypotension of less than 70 mm Hg for more than 30 min correlates with a mortality of 60%,[151] yet allowing a systolic pressure of 50–70 mm Hg in arteriopaths with ruptured abdominal aortic aneurysms produced very good results.[28] In reality, trauma patients represent a spectrum of pathology and what is ideal treatment for one is inadequate for another. Ideally, we should differentiate between uncontrolled and controlled haemorrhagic shock. In uncontrolled haemorrhagic shock control of bleeding has not occurred, haemorrhage is ongoing and aggressive i.v. fluid therapy is likely to increase bleeding. Rapid surgical control of haemorrhage is the priority; sufficient fluid resuscitation to ensure viable survival should be given until haemorrhage is controlled. The great difficulty comes in the translation of these ideals into procedures that can be followed by ambulance personnel. How does the paramedic know which trauma patient has uncontrolled haemorrhage and which does not. Ambulance services are very aware of current thoughts on trauma patient management and are already striving to reduce pre-hospital times. The Staffordshire Ambulance Service NHS Trust strongly encourages its paramedics to insert i.v. cannulae en route, rather than at the scene, unless the patient is trapped. Furthermore, fluid therapy is targeted to maintaining a radial pulse only (C. Carney, personal communication).

When the patient has received definitive care and haemorrhage has been controlled, the goals of resuscitation shift to optimization of oxygen delivery (see below). In clinical practice separation of these two phases may be indistinct because continued haemorrhage may not be definitively controlled by surgery alone and the ischaemic insult before haemorrhage control may determine long-term outcome.

Communication

Communication is vital in providing an efficient link between pre-hospital and in-hospital trauma patient resuscitation. The importance of having advanced warning before arrival of a severely injured patient in the accident department cannot be overstated. Ideally, the ambulance officer at the scene should be able to communicate directly with accident department staff via a talk-through link. This provides concise and essential information on the patient's condition and the estimated time of arrival at hospital. Accident department staff can then decide whether to alert individual specialists or, if it exists, the trauma team. Many hospitals have specific criteria for a trauma team call. With advance warning, medical and nursing staff can prepare a resuscitation bay for the patient's arrival.

In-hospital resuscitation

ADVANCED TRAUMA LIFE SUPPORT

A considerable advance in trauma patient resuscitation has been made by the introduction of the advanced trauma life support (ATLS) in the UK in the latter half of 1988.[96] Unfortunately, this is very difficult to prove and only one group has documented a reduction in trauma mortality after the introduction of ATLS.[34] The ATLS course manual and slides are produced by the Committee on Trauma of the American College of Surgeons (ACS).[135] By its very nature, the course is didactic and an identical core content is taught to all doctors on ATLS courses across the world. Not unexpectedly, this has led to a certain amount of criticism, particularly from British anaesthetists.[9] For example, earlier editions of the ATLS manual strongly promoted blind nasal intubation, a concept that was never accepted by UK anaesthetists.[153] The UK ATLS Committee has had some influence on later versions of the manual and the approach to these controversial areas has been rationalized. ATLS provides a useful framework on which we can base our resuscitation efforts. Although the course is aimed at the single-handed physician working in a rural hospital, the ATLS procedures can be adapted easily for a team approach. It is testament to the perceived use of ATLS that since its introduction to the UK more than 9000 individuals have attended a provider course and there are now 621 ATLS instructors (O. Egerton, personal communication). Incidentally, in the UK, anaesthesia is represented by more ATLS instructors than any other specialty. More information on ATLS can be received from the ATLS office, Raven Education Department, RCS (tel. 0171 973 2102, fax 0171 973 2117, E-mail atls@rcseng.ac.uk).

The ATLS course focuses on the initial management of patients with major injuries during the so-called "golden hour". Donald Trunkey has described previously the trimodal distribution of trauma patient deaths.[139] The first peak of death is within seconds to minutes of injury (e.g. severe head and chest trauma) and only measures to prevent trauma will reduce it. The second peak of death, the early deaths, are those dying, for example, from intracranial haemorrhage and multiple injuries with hypovolaemia; timely and appropriate resuscitation of these patients should reduce mortality. The third peak of death represents those patients dying, a few weeks later, from sepsis and multiple organ failure. Appropriate management of the patient in the resuscitation phase, with rapid restoration of cellular oxygenation, should also reduce this third peak of deaths. The classic "trimodal" distribution of trauma patient deaths has been challenged recently,[117 155] but this should not detract from the philosophy of rapid, systematic and appropriate management.

Table 2 Composition of a typical trauma team

- Team leader—primary and secondary surveys, co-ordination of team, overall responsibility for the patient while in the A&E department.
- Anaesthetist—airway, ventilation, central venous access, difficult peripheral access, fluid balance, analgesia
- Other doctor—all other procedures, chest drain, fracture splintage, urethral catheter
- Nurses x 2—measure vital signs, record data, remove clothes, assist doctors.
- Radiographer—cervical spine, chest and pelvic x-rays, other x-rays as requested by team leader.
- Porter—to take samples to pathology labs, to retrieve urgent blood from blood bank.

Table 3 The role of the trauma team leader[99] (reprinted with permission)

- To offer advice to any hospital wishing to discuss or refer a patient, and to accept appropriate referrals
- To obtain a history from the ambulance staff (for direct admissions) or from the referring doctor and medical escort (for transferred patients)
- To examine the patient (performing primary and secondary surveys)
- To establish the priorities for investigation and intervention
- To co-ordinate the trauma team
- To maintain an overview, avoiding undue involvement in practical procedures, but intervening appropriately in critical situations.
- To supervise the administration of fluids, blood and blood products.
- To provide analgesia
- To request and interpret investigations in conjunction with other team members
- To consult with or refer to other specialists where appropriate, indicating any perceived needs for urgent intervention
- To supervise spinal precautions
- To supervise the patient during transfer within the hospital and during imaging procedures
- To co-ordinate the assignment of the consultant responsible for continuing care
- To arrange transfer to the operating theatre, intensive care unit or other ward area (or to another hospital when indicated), and to provide a detailed hand-over to their staff
- To review the patient subsequently to help maintain continuity
- To inform the family
- To excuse the trauma team members at the end of the resuscitation, and to debrief the team after difficult cases
- To make a detailed note in the patient's records and to record agreed information for audit.

THE TRAUMA TEAM

Trauma patient resuscitation is most efficient if undertaken by a team of appropriately trained doctors and nurses.[35] In this way a variety of tasks can be undertaken simultaneously, a process known as "horizontal organization". The precise composition of the team inevitably varies from one hospital to another. The composition of a typical team and the team members' roles are listed in table 2. The role of the team leader is particularly important and has been defined comprehensively by a British

Table 4 The primary survey

1. Airway with cervical spine control.
2. Breathing with ventilatory support
3. Circulation and haemorrhage control
4. Disability—a rapid assessment of neurological function
5. Exposure—while considering the environment, and preventing hypothermia

Trauma Society Standards Working Party (table 3).[99] These standards represent the ideal and are probably achievable only by hospitals with relatively large trauma units. Nevertheless, many hospitals have worked hard to create a system that brings senior, experienced clinicians into the trauma resuscitation room before, or soon after, admission of a seriously injured patient.

PRIMARY SURVEY AND RESUSCITATION

The initial resuscitation of the trauma patient entails the primary survey, simultaneous resuscitation and identification of those injuries that require immediate surgery. The aim of the primary survey is to look systematically for immediately life-threatening injuries, in the order that they are most likely to kill the patient (table 4). If life-threatening problems are detected they are treated immediately, before proceeding to the next step of the primary survey. A head-to-toe examination of the patient is not undertaken until the patient's vital signs have been stabilized.

Airway and cervical spine

Every patient sustaining significant blunt trauma, particularly above the clavicles, should be assumed to have a cervical spine injury until proved otherwise. These patients should have the cervical spine immobilized with a semi-rigid cervical collar and bilateral sandbags or blocks joined with tape or straps across the forehead (fig. 1)[106] or by manual in-line stabilization (MILS). If the patient has an unstable cervical spine injury, further movement may cause or worsen injury to the cord. Thus all airway manoeuvres must be performed carefully, and without moving the neck.[6 15 30 55 86 141] The cervical spine cannot be deemed undamaged until the patient has been examined by an experienced clinician *and* appropriate radiological procedures have been completed.[154] A reliable clinical examination cannot be obtained if the patient has sustained a significant closed head injury, is intoxicated or has a reduced conscious level from any other cause.

In the unconscious patient, or in the presence of haemorrhage from maxillofacial injuries, the airway is best secured by placing a cuffed tube in the trachea. Other reasons for intubating the trachea of a trauma patient during the resuscitation phase are to improve oxygenation and control ventilation, and to allow appropriate procedures to be performed on uncooperative patients. For example, in the case of the combative, intoxicated trauma patient with head and other potentially severe injuries, induction of anaesthesia and intubation facilitate definitive investigation (e.g. CT scan) and prevent secondary injury (self-inflicted trauma and secondary brain injury from hypoxia, hypercapnia, hypotension and hypertension). There is increasing evidence that, if performed with care, tracheal intubation of a patient with a cervical spine injury carries relatively little risk.[30] However, uncontrolled intubation in a patient with an unstable cervical spine injury can result in serious damage to the spinal cord.[53] Thus a sensible approach to airway management of patients with known mechanisms of injury is to initially treat all of them as if they had an unstable cervical spine injury, even if the initial plain films are normal.[131]

The technique of choice for emergency tracheal intubation in a patient with a potential cervical spine injury is direct laryngoscopy and oral intubation with MILS, after a period of preoxygenation, i.v. induction of anaesthesia, paralysis with suxamethonium and application of cricoid pressure (fig. 2).[29 152] Placing the patient's head and neck in neutral alignment tends to make the view at laryngoscopy

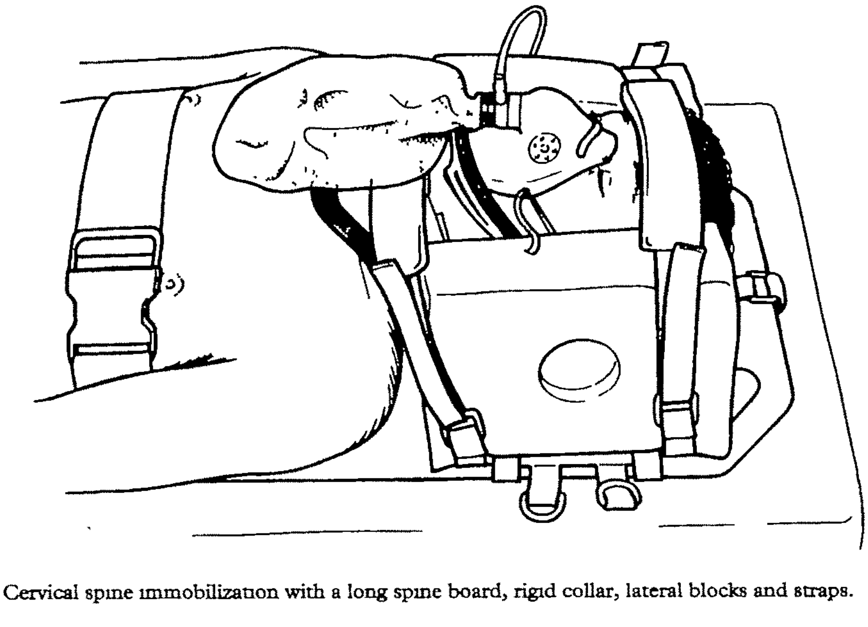

Figure 1 Cervical spine immobilization with a long spine board, rigid collar, lateral blocks and straps.

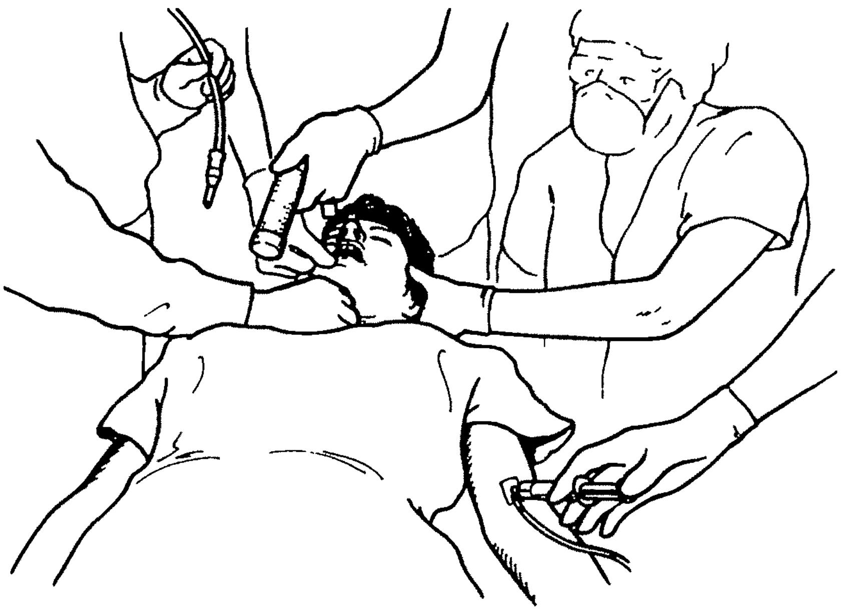

Figure 2 Rapid sequence induction of anaesthesia and manual in-line cervical stabilization in an acute trauma patient.

worse,[54] but intubation is aided greatly by the use of a gum-elastic bougie.[57 97] If intubation of the patient's trachea proves impossible, a laryngeal mask[49 104] may provide temporary oxygenation and ventilation while surgical cricothyroidotomy is performed.

Smooth induction of anaesthesia and neuromuscular block provide optimal conditions for intubation in high-risk patients. All anaesthetic induction agents are vasodepressors and respiratory depressants, and have the potential to produce or worsen hypotension. There is no evidence that the choice of induction agent alters survival in major trauma patients. Their appropriate use during resuscitation involves careful assessment of the clinical situation and thorough knowledge of their clinical pharmacology. The safest strategy is for the anaesthetist to use agents with which he or she is familiar; the trauma resuscitation room is not the place for experimentation. Major trauma patients are at significant risk of awareness.[16] Anaesthetic requirements need to be judged, as always, on an individual basis and the risk of awareness kept to a minimum. Severely injured patients requiring intubation generally fall into three groups: (a) patients who are stable and adequately resuscitated; they should receive a standard or slightly reduced dose of induction agent, (b) patients who are unstable or inadequately resuscitated but require immediate intubation; they should receive a reduced, titrated dose of induction agent (in this situation factors such as best guess, skill and experience come into play), and (c) patients who are in extremis, and are severely obtunded and hypotensive; here induction agents would be inappropriate but neuromuscular blocking agents may be used to facilitate intubation. As soon as adequate cerebral perfusion is achieved, anaesthetic and analgesic drugs should be administered.

Suxamethonium retains its status as the neuromuscular blocker with the fastest onset of action, and remains the first choice blocker for intubation of the acute trauma patient. The concerns that suxamethonium may cause an increase in ICP in severe head-injured patients appears to be overstated provided adequate anaesthesia is provided.[20 75] Rocuronium is almost as fast in onset and is favoured by many trauma anaesthetists.[84] In the US, before the availability of rocuronium, vecuronium was a popular choice for use in acute trauma patients.[98]

Circulation

After arrival in hospital, failure to maintain an effective circulation remains the leading cause of death in severely injured patients.[59]

I.v. access. Severely injured patients require at least two large-bore i.v. cannulae. If peripheral placement of these cannulae is impossible percutaneously, other options include: cut-down on a peripheral vein, percutaneous femoral cannulation, central venous cannulation or the intraosseous route. Cut-downs have few complications and can be performed quickly with minimal training. Possible cutdown sites include: the antecubital fossa, saphenous vein at the ankle and proximal saphenous vein. Most anaesthetists are more familiar with the Seldinger technique for placement of large bore cannulae and this choice is supported by a multicentre, prospective, randomized study comparing i.v. access by saphenous cutdown with percutaneous femoral cannulation.[150] In a total of 78 trauma patients, the mean time for cut-down (5.6±2.6 min) was significantly longer than that required for percutaneous femoral cannulation (3.2±1.2 min). The main disadvantage of the percutaneous femoral approach is that it requires a palpable femoral arterial pulse. Internal jugular or subclavian access is preferred by many anaesthetists but central venous access may not be easy in the hypovolaemic patient and there is a risk of creating a pneumothorax. If the central route is used, a 8.5-French gauge pulmonary artery introducer sheath is ideal for rapid fluid resuscitation.

The intraosseous route[118] (usually via the proximal tibia) is useful in children but, using conventional fluids, does not allow high enough flow rates for effective fluid resuscitation in adults. However, there is a possibility of infusing hypertonic intraosseous fluids in adults.[79]

Fluid warming. All i.v. fluids should be warmed properly. A high capacity fluid warmer, such as the Level 1,[21 95] is required to cope with the rapid infusion rates used during trauma patient resuscitation. Hypothermia (core temperature less than 35 °C) is a serious complication of severe trauma and haemorrhage.[82] The aetiology of hypothermia in the patient requiring massive transfusion is multifactorial and includes exposure, tissue hypoperfusion and infusion of inadequately warmed fluids. In trauma patients hypothermia correlates with survival; those with a core temperature decreasing to less than 34 °C have a 40% mortality compared with a 7% mortality for those whose lowest recorded core temperature is 34 °C or above.[71] Hypothermia has several adverse effects:

- the oxyhaemoglobin dissociation curve is shifted to the left, thus impairing peripheral oxygen delivery in the hypovolaemic patient at a time when it is most needed
- shivering may compound lactic acidosis which typically accompanies hypovolaemia and this may be aggravated further by decreased metabolic clearance of lactic acid by the liver
- it contributes to the coagulopathy accompanying massive transfusion.[102] The likely mechanisms involved include: retarding the function of enzymes in the clotting cascade[111] enhanced plasma fibrinolytic activity[103]; and reduced platelet aggregation.[142] Recent studies have shown that bleeding time and prothrombin time, in particular, are prolonged by hypothermia.[101 129 143]

Care must be taken with some of the more powerful warming and rapid infusion systems. There is a potential for rapid circulatory overload unless patients are monitored appropriately and continually.[52]

Principles of fluid management emphasize that restoration of intravascular volume should be fast and efficient. Recognizing that anaemia is tolerated better than hypovolaemia allows the initial fluid resuscitation to be non-blood. While the choice of fluid may be less important than the speed and adequacy of volume replacement, the increasing variety of fluids available tends to confuse the issue. Resuscitation fluids currently available include: isotonic crystalloids (sodium chloride, Hartmann's solution, Ringer's lactate solution), hypertonic saline with or without a colloid component, gelatin solutions (polygeline, succinylated gelatin), etherified starch solutions (hetastarch, hexastarch, pentastarch), dextrans and blood. Haemoglobin solutions are undergoing clinical studies and will be available in the near future.

Colloids vs crystalloids. The crystalloid *vs* colloid debate continues and for reasons discussed below, is unlikely to be resolved. As an increasing number of colloids become available, the controversy may evolve into which colloid *vs* crystalloid.[138] There are some areas of agreement between the opposing views. Most agree that colloids are more efficient in that equivalent intravascular volume expansion is achieved with less colloid. Colloids are more expensive than crystalloids. There is no risk of anaphylaxis with crystalloids. Colloid oncotic pressure is better maintained with colloid. Fluid overload is bad for the patient regardless of the type of fluid used. The amount of interstitial oedema is dependent on the volume of fluid given and there is a negative correlation between a positive fluid balance and survival in critically ill patients.[90] As it takes 2–6 times the volume of crystalloid compared with colloid to maintain the same haemodynamic state in critically ill patients,[64] it is not surprising that crystalloid fluid resuscitation causes greater interstitial oedema. In theory, interstitial oedema has several adverse effects:

- cerebral: obtunded conscious level
- pulmonary: impaired gas exchange
- myocardial: reduced compliance
- tissue: impaired wound healing
- gut: reduced absorption and enhanced bacterial translocation

Despite these reservations, no prospective, randomized studies have demonstrated clearly the superiority of colloids over crystalloids for trauma resuscitation. Double-blind studies with the power to define any advantages are unlikely given the complexity of trauma cases and the difficulty in establishing matched controls. There is also great difficulty in deciding the most appropriate endpoints for such studies. Should it be survival or duration of hospital or ICU stay, or the incidence of organ failure? Other variables, such as age, ISS and pre-injury pathology, are inevitably greater discriminators of outcome than the choice of resuscitation fluid.

Crystalloids. The American College of Surgeons' ATLS committee recommends the use of lactated Ringer's solution for the initial resuscitation of severely injured patients.[135] The use of normal saline may cause a hyperchloraemic acidosis and may compound any underlying pathological acidosis.[83] Part of the rationale for using crystalloids is that trauma patients have sustained considerable interstitial fluid losses and intravascular loss. An alternative explanation is that gelatin solutions are not available in the USA, and alternative colloid solutions such as starch and albumin would be expensive or limited by the volume that can be infused.

Gelatin solutions. Gelatins are the only cheap colloid available that can be infused in unlimited volumes, they have no effects on the cross matching of blood and act as an osmotic diuretic. While it has been suggested that in comparison with saline, fluid resuscitation with gelatin solution prolongs bleeding time,[40 87] the case is far from proved and further study is required.

Hydroxyethyl starch solutions. Hydroxyethyl starch solutions are synthetic polymers derived from amylopectin. Different degrees of substitution of hydroxyethyl groups for glucose result in solutions of varying properties. HES 450/0.7 has an average molecular weight of 450 000 Da and a high molar substitution ratio (0.7). This solution has a long half-life (more than 24 h) and results in prolonged haemodilution. The fact that it accumulates in the reticuloendothelial system has not yet been shown to cause problems. It also causes a coagulopathy via an effect on factor VIII and von Willebrand factor.[72] For these reasons the maximum dose of high molecular weight HES is restricted to 20 mg kg^{-1} day^{-1} and it cannot be recommended for trauma patient resuscitation. Pentastarch (HES 200/0.5) is diafiltered to produce a more homogenous solution (10–1000 kDa) which has a lower weight average and a half-life of approximately 6 h. Animal studies suggest that these medium weight HES solutions may be capable of plugging leaky capillaries in inflammatory states.[146,149,158] Pentafraction (100–500 kDa) is even more homogenous than pentastarch and is the most effective at reducing transvascular leak.[92,109] Hydroxyethyl starch encourages restoration of macrophage function after haemorrhagic shock.[120] A recent study of trauma and sepsis patients showed that 10% HES (200/0.5) resulted in significantly better systemic haemodynamics and splanchnic perfusion than volume replacement with 20% human albumin.[17] Although the medium weight starch solutions appear very attractive for resuscitation from haemorrhagic shock, the fact that they are expensive and can cause anaphylaxis may temper our enthusiasm.[78,93]

Hypertonic saline solutions. Hypertonic crystalloid solutions are attractive as they provide small volume resuscitation and rapid restoration of haemodynamics with laboratory evidence of improved microcirculatory haemodynamics.[79] They exert their effect by recruitment of interstitial volume thus increasing circulating volume and increasing arterial pressure. However, as discussed above, increasing arterial pressure may not always be an ideal goal, and their role in trauma resuscitation has yet to be defined. Many clinical studies are now using small volumes of highly hypertonic solutions (7.5% saline) for pre-hospital resuscitation.[36,89,145] These studies have yet to show a clear improvement in survival as the primary end-point.[77] However, in a subset of head-injured patients with a Glasgow coma scale score of 8 or less, survival to hospital discharge was higher in patients receiving hypertonic saline (with or without dextran 70) compared with those receiving Ringer's lactate.[145] The potential for benefit in head-injured patients is not surprising in that small changes in serum sodium exert much greater effects on serum osmolality, and therefore on brain water and intracranial pressure, than do changes in colloid oncotic pressure.[159] However, hypernatraemia may induce its own problems; administration of large volumes of hypertonic saline to patients with burns resulted in a four-fold increase in acute renal failure and a two-fold increase in mortality.[61]

Blood and haemoglobin solutions. Blood, while being the ideal replacement for haemorrhage, is expensive, in short supply, antigenic, requires cross matching, has a limited shelf life, requires a storage facility and carries a risk of disease transmission. It is well known that blood transfusion has an immunosuppressive effect and one study showed that the volume of blood infused and injury severity score were the only two significant predictors of infection.[2] However, this phenomenon is more likely to be a reflection of the duration and severity of shock.[119]

Having overcome several problems related to toxic stroma, short intravascular half-life and high colloid osmotic pressure, a number of haemoglobin solutions are now at advanced stages of development.[27a,33,70,110] In a rat model of haemorrhagic shock, diaspirin cross-linked haemoglobin (DCLHb) was more effective in restoring tissue perfusion and improving survival than lactated Ringer's solution or 7.5% hypertonic saline.[80] DCLHb has been given to patients undergoing elective abdominal aortic repair[45] and to patients with sepsis syndrome.[113] It has a significant vasopressor effect which is thought to result from binding nitric oxide and from an effect on adrenergic receptors.[122] In 76 human volunteers, genetically engineered haemoglobin (rHb1.1) also produced a transient increase in arterial pressure and studies are underway in anaesthetized patients.[70] The potential for using haemoglobin solutions to resuscitate trauma patients, particularly in the pre-hospital phase, is very exciting. An increase in mean arterial pressure, in conjunction with decreased viscosity of haemoglobin solutions, may result in significantly better oxygen delivery to vital organs. In a rat model of controlled haemorrhage, DCLHb was superior to crystalloid, albumin and blood in gut resuscitation.[42] The potential disadvantages in increasing arterial pressure in uncontrolled haemorrhage (as discussed above) have still to be considered. Furthermore, the long-term safety of massive transfusion with haemoglobin solutions in humans has yet to be demonstrated.

What is the optimal packed cell volume (PCV) in the acute trauma patient? Hypovolaemia is tolerated considerably less well than anaemia. Traditional teaching is that all patients require a PCV of 30% or a haemoglobin concentration of 10 g dl^{-1} for optimal oxygen delivery. However, normovolaemic patients with good cardiopulmonary function tolerate haemoglobin concentrations as low as 7 g dl^{-1}.[94] In a small, randomized pilot study, the mortality of a group of critically ill patients with haemoglobin concentrations maintained at 7–9 g dl^{-1} was no different to a group with concentrations of 10–12 g dl^{-1}.[58] Provided normovolaemia is achieved the reduction in viscosity results in a significant increase in cardiac output[127] and tends to improve tissue oxygenation.[144] The problem is that during resuscitation of the acute trauma patient, a history of ischaemic heart disease or significant respiratory disease may not be available. Furthermore, the haemoglobin concentration of a haemorrhaging patient undergoing resuscitation is changing rapidly. Under these conditions the margin of safety is very small if the haemoglobin concentration is reduced to as low as 7 g dl^{-1} even if the patient is previously healthy. As part of the systemic inflammatory response syndrome, the severely injured patient has an increased oxygen requirement and therefore it would be unwise to chose a "transfusion trigger" on the basis of data that have been obtained from stable anaesthetized patients. Until more data are available from studies on critically ill patients, the haemoglobin concentration of severely injured patient should be targeted at around 10 g dl^{-1} However, in the confirmed cardiovascularly healthy trauma patient with only moderate injuries, a haemoglobin value as low as 7 g dl^{-1} may be acceptable.

Monitoring

By any definition, major trauma patients are critically ill and it is entirely appropriate to provide monitoring in the emergency department which is to the same standard as that in the intensive care unit. Arterial cannulae and central venous catheters should be inserted as soon as possible. Small, portable monitors that display ECG, invasive arterial pressure, oxygen saturation, central venous pressure, end-tidal carbon dioxide and temperature are available widely and should be used in all major trauma patients.

Resuscitative thoracotomy

Resuscitative thoracotomy may be a life-saving procedure. However, it is a high-risk procedure for those individuals involved in resuscitation and should not be undertaken in futile cases. The surgical skill and facility required should be available in the resuscitation area of all hospitals that receive major trauma patients on a regular basis. The indications for emergency resuscitative thoracotomy include:

- control of intrathoracic haemorrhage
- relief of cardiac tamponade
- electromechanical dissociation after penetrating trauma
- uncontrollable haemorrhage below the diaphragm where cross-clamping the thoracic aorta allows haemorrhage control
- control of a massive air leak.

Of 423 patients undergoing emergency thoracotomy, the overall survival rate was 13%.[81] Survival after penetrating injury was 22% (8% survival after gun shot wound and 34% after stab wound) but only 2% after blunt trauma. The authors concluded that emergency thoracotomy is not indicated if there are no signs of life on initial pre-hospital assessment. Although survival from this procedure after penetrating injury is reasonably good, it is rarely beneficial for the victim of blunt trauma.[8,38,60]

Resuscitation end-points

When haemorrhage control has been achieved, the goals of resuscitation are to optimize oxygen delivery and improve microcirculatory perfusion to facilitate the repair process. Patients with severe injuries have high oxygen requirements immediately, and rapidly accumulate a significant oxygen debt, as indicated by high blood lactate concentrations and an increasing base deficit.[37] Shoemaker and colleagues have demonstrated a reduction in mortality in a variety of high-risk surgical patients using therapy targeted to achieve supranormal values for cardiac index (CI) (>4.5 litre min^{-1} m^{-2}), oxygen delivery index ($D\mathrm{O}_2\mathrm{I}$) (>600 ml min^{-1} m^{-2}) and oxygen consumption index ($\dot{V}\mathrm{O}_2\mathrm{I}$) (>170 ml min^{-1} m^{-2}).[123] More recently, investigators have examined the potential benefit of goal-directed therapy, specifically in trauma patients.[13,14,91] There is little doubt that failure to achieve supranormal values of $D\mathrm{O}_2\mathrm{I}$ and $\dot{V}\mathrm{O}_2\mathrm{I}$ is a strong predictor of multiple organ failure and death,[14,91] while the standard haemodynamic measurements of MAP and CVP fail to differentiate between survivors and non-survivors.[14] What we really need to know, however, is whether we can improve outcome by striving to achieve these goals. A recent study in patients with predominantly penetrating injuries showed that mortality can be reduced by targeting the following resuscitation goals: CI>4.5 litre min^{-1} m^{-2}, $D\mathrm{O}_2\mathrm{I}$ >670 ml min^{-1} m^{-2} and $\dot{V}\mathrm{O}_2\mathrm{I}$ >166 ml min^{-1} m^{-2}.[13] This approach to the trauma patient requires insertion of a pulmonary artery floatation catheter and some authors have suggested that this should be placed early in the resuscitation process.[1]

Recent evidence has suggested that aggressive efforts to increase $D\mathrm{O}_2\mathrm{I}$ in critically ill patients may be detrimental.[56] Another study of goal-directed therapy in a group of predominantly trauma patients failed to show any difference in the incidence of organ failure or death.[39] The current popular approach to fluid resuscitation of severe trauma patients is to increase $D\mathrm{O}_2\mathrm{I}$ with appropriate fluid resuscitation and moderate doses of dobutamine (up to 20 μg kg^{-1} min^{-1}), while monitoring mixed venous oxygen saturation ($S\bar{v}_{\mathrm{O}_2}$), base deficit and/or blood lactate concentration.[88]

Several investigators have criticized the use of global oxygenation indices to detect the presence of tissue dysoxia and a recent consensus conference has addressed these issues.[137] It is possible to have regional ischaemia that would not necessarily be reflected by a change in $\dot{V}\mathrm{O}_2\mathrm{I}$ or plasma base deficit.[50,51] The splanchnic bed is the first region to be rendered ischaemic during shock, and after resuscitation is the last to have perfusion restored to normal. Gastric mucosal pH (pH_i) is monitored using a gastric tonometer[41] and correlates well with intestinal oxygen consumption and hepatic venous $P\mathrm{O}_2$, lactate and outcome.[34] pH_i may be a better resuscitation goal in trauma patients than $D\mathrm{O}_2\mathrm{I}$ and $\dot{V}\mathrm{O}_2\mathrm{I}$.[65] The standard technique of gastric tonometry using a saline-filled balloon is rather laborious and allows only intermittent measurement of pH_i; partly for this reason it is infrequently used in clinical practice. New developments in gastric tonometry allow continuous measurement of pH_i either from an air-filled balloon connected to a modified capnometer ("capnometric recirculating gas tonometry") or by directly measuring luminal $P\mathrm{CO}_2$ with a fibreoptic $P\mathrm{CO}_2$ probe.[44,74]

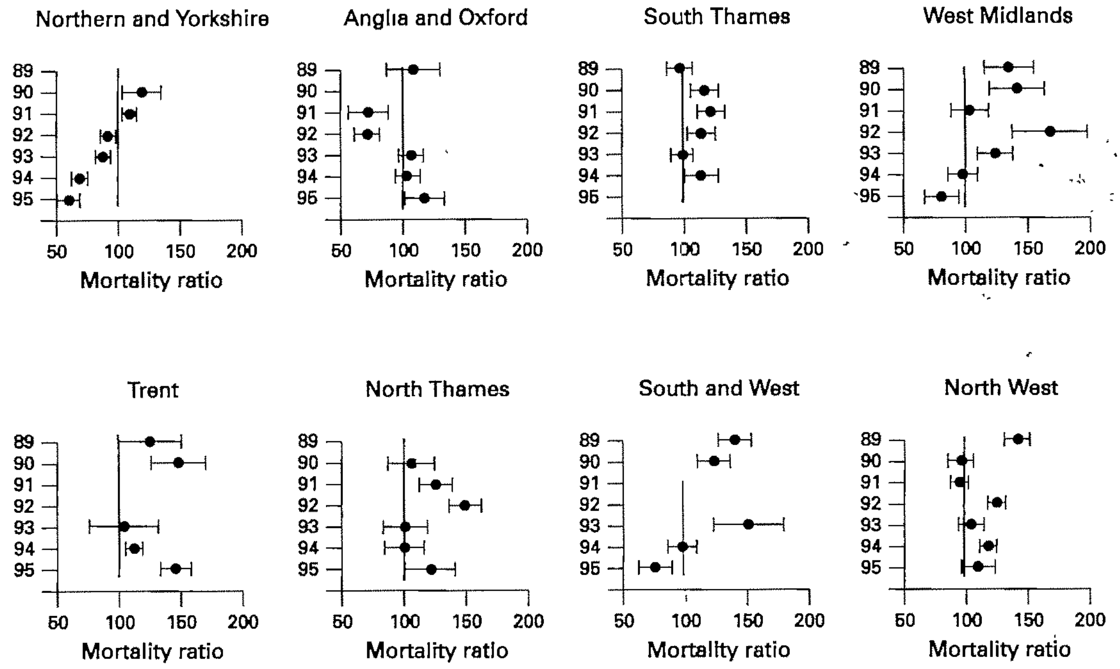

Figure 3 Mortality ratios (±1 SEM) for major trauma patients from 1989 to 1995, by region. Reproduced with kind permission from Maralyn Woodford, National Co-ordinator for the UK Trauma Audit and Research Network.

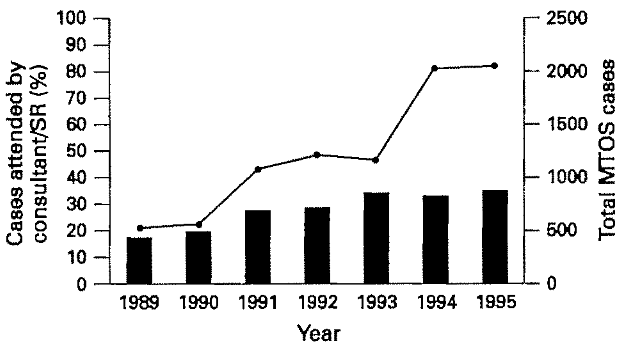

Figure 4 Proportion of severely injured patients seen first by consultants or senior registrars (columns) and total number of cases from the Major Trauma Outcome Study (MTOS) (line), by year. Reproduced from data provided by Maralyn Woodford, National Co-ordinator for the UK Trauma Audit and Research Network.

The UK Trauma Audit and Research Network

The Major Trauma Outcome Study (MTOS) (UK) has been collecting data on seriously injured patients for 8 yr. There are 86 000 patients on the database and 117 hospitals in the UK have enrolled with MTOS.[136] Last year MTOS (UK) changed its name to the UK Trauma Audit and Research Network and formed links with the Cochrane Centre and the NHS Centre for Reviews and Dissemination. It is hoped that this will facilitate the development of evidence-based guidelines for the management of major trauma. On the basis of the data collected so far, MTOS participating hospitals have good cause for optimism. Between 1988 and 1996 the overall mortality ratio (the observed number of deaths divided by the expected number of deaths x 100) has improved from 124 to 97 (fig. 3). Over the 7-yr period 1989–1995, after severity of injury is controlled for, the odds of death in children and young adults (less than 24 yr) after severe injury declined by 16% a year.[114] It is not possible to identify with certainty which of the many facets of trauma patient management have contributed to this apparent improvement in outcome. However, it is likely that developments in assessment and resuscitation techniques, many of which have been discussed above, are major factors. One certain fact is that the proportion of seriously injured patients seen first by consultants or senior registrars has increased from 17% in 1988 to 30% in 1995[136] (fig. 4). In the context of the debate on pre-hospital trauma management, it is of some concern that pre-hospital times have increased from a mean of 37 min in 1988 to 58 min in 1995. Bearing in mind that during this period there was no change in the number of trapped patients or in the distribution of injury severity, we must establish the specific effect of this trend on outcome. Perhaps the Medical Care Research Unit pre-hospital study[62] will provide some answers.

The International Trauma Anaesthesia and Critical Care Society (ITACCS)

In 1988 a group of enthusiasts in Baltimore established ITACCS. The society holds an annual symposium, numerous seminars, offers research grants and has been responsible for several publications on trauma anaesthesia and critical care. More than 1000 members from 44 countries exchange and develop ideas on all aspects of trauma anaesthesia, resuscitation and critical care. Information on the society can be obtained from ITACCS World Headquarters, PO Box 4826, Baltimore MD 21211 USA (Fax +1 410 235 8084).

Conclusion

Several deficiencies highlighted by the 1988 Royal College of Surgeons Working Party Report on the management of patients with major injuries have been addressed and there is some evidence that developments in trauma patient management have improved outcome. The principles outlined above provide the basis for making rational decisions in trauma resuscitation. There is no substitute for training, experience, good communication and team work if resuscitation of the trauma patient is to be completed rapidly and effectively. Trauma continues to be the most common cause of death in the first four decades of life and as part of a multidisciplinary team, the trauma anaesthetist must strive to reduce this mortality.

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Uniform reporting in resuscitation

W. F. DICK

Over the past 20 yr resuscitation medicine has become a scientifically recognized interdisciplinary part of acute medicine. However, the two main areas of resuscitation medicine—cardiopulmonary–cerebral resuscitation (CPCR) and trauma life support (TLS)—are still practised under entirely different conditions and circumstances. As a result, data on quality of care, quality of outcome and life after survival, in addition to many other criteria, differ from publication to publication.[7 8 19 24 26 29]

In 1974 the American Heart Association (AHA) published the first edition of "standards for CPR".[1] Many changes were made to subsequent versions of the standards, later to be termed guidelines, because a considerable number of conclusions made in 1974,[1] 1980,[2] 1986[3] and 1992[4] had never been scientifically proved. This was because uniform criteria had not been established to describe the study design of animal and human CPR research projects, to report the characteristics of the emergency medical services (EMS) systems and outcome data.

Consequently, the CPR Research Committee of the European Academy of Anaesthesiology (EAA) met in 1986 to discuss and develop recommendations for animal research in CPR; these were published initially in 1988,[14] followed by a revised version in 1990.[15] Recommendations for clinical CPR studies[15] were published by the same group later that year.

The topics for animal research discussed by the committee included: type of animal; anaesthetic technique; methods of induction and duration of cardiac arrest; CPR technique; ventilation volumes; use of buffers, inotropes and antiarrhythmic agents; and monitoring.

The following topics were included in the recommendations for clinical studies: prospective, randomized studies; patient data; distinction between witnessed and unwitnessed cardiac arrest, and cardiorespiratory and cardiocirculatory arrest; out-of-hospital and in-hospital arrests; VF/VT, asystole and EMD; drugs and routes of administration; monitoring; level of training of responders; pre-arrest conditions; survival after different intervals (outcome); quality of life after survival.

These reports, together with similar initiatives by experts from the American Heart Association,[1 2 3 19 20] European Resuscitation Council (ERC), Heart and Stroke Foundation of Canada (HSFC), Australian Resuscitation Council (ARC) and Resuscitation Council of South Africa (RASC) were the background for an informal gathering by experts from these organizations at Utstein Abbey on the Norwegian Island of Mosteroy in the summer of 1990. At this meeting it was decided to hold a scientific conference on the subject of developing guidelines for uniform reporting of data from cardiac arrest.[11]

The Utstein Consensus Conference was convened near London later that year and members of the organizations participating in the first Utstein symposium were invited. A template was developed to include the most relevant factors for describing and comparing CPR research results. This template was described as the Utstein style after the site of the initial meeting.

Uniform reporting of data—the Utstein style

The term Utstein style has been incorporated into the following templates:

- a template for out-of-hospital resuscitation[8]
- a template for paediatric resuscitation[32]
- a template for in-hospital resuscitation[9]
- a disaster medicine response research template[30]
- a template for reporting laboratory research in animals.[22]

In 1995 Spaite and colleagues[28] reported the results of the US Prehospital Emergency Medical Services Data Conference which provided the basis for an 81-item uniform data set. It was hoped that documentation conforming to this template would answer the question, "has the EMS (apart from out-of-hospital cardiac arrest and resuscitation) had an impact on morbidity and mortality of emergency patients (trauma, intoxication, asthma, myocardial infarction, etc).

Another template for uniform reporting of data after trauma is under development and others may follow.[16 17]

(*Br. J. Anaesth.* 1997; **79**: 241–252).

Key words
Heart, resuscitation. Complications, cardiac arrest. Records, Utstein template.

W. F. DICK, MD, Clinic of Anaesthesiology, University Hospital, Mainz, Langenbeckstr. 1 D 55131, Mainz, Germany.

UNIFORM REPORTING OF DATA AFTER OUT-OF-HOSPITAL CARDIAC ARREST

Terminology

The working group initially focused on developing a uniform and worldwide acceptable terminology set down in a "glossary of terms".

The *glossary of terms* begins with a definition of a cardiac arrest and its aetiology (cardiac, non-cardiac). It also outlines major signs and symptoms, regardless of how long they may persist.

A consensus was established as to what was to be included under the headings basic life support (BLS), advanced life support (ALS), basic cardiopulmonary resuscitation (BCPR) and advanced cardiopulmonary resuscitation (ACPR). The following definitions relating to the treatment of cardiac arrest were agreed.

BCPR includes expired air inflation of the lungs with and without airway adjuncts and face shields (excluding the use of bag–valve–mask devices, laryngeal mask airway, oesophageal tubes/Combitubes or tracheal tubes) and application of external thoracic compression. In the USA, in contrast with European practice, BLS includes knowledge of public access to the EMS system and an educational programme, in addition to technical skills in BCPR

ACLS and ACPR are very similar and include intubation, defibrillation and medication. Defibrillation may become part of BLS in several countries in the future, particularly to take into account the increasing use of automatic external defibrillators (AED).

A distinction was made on the basis of the qualification of initial CPR providers to differentiate between bystander CPR performed by lay responders compared with professional first responders who are either part of the emergency medical system (EMS) or acting as a bystander.

Times, events, intervals

Precise definitions of events, times and event-to-event intervals were made. Some of this information was deemed essential (core data); other data were considered optional (supplementary data). The following example indicates the relationship between events, times and intervals (figs 1, 2).

CARDIAC ARREST

Collapse occurs

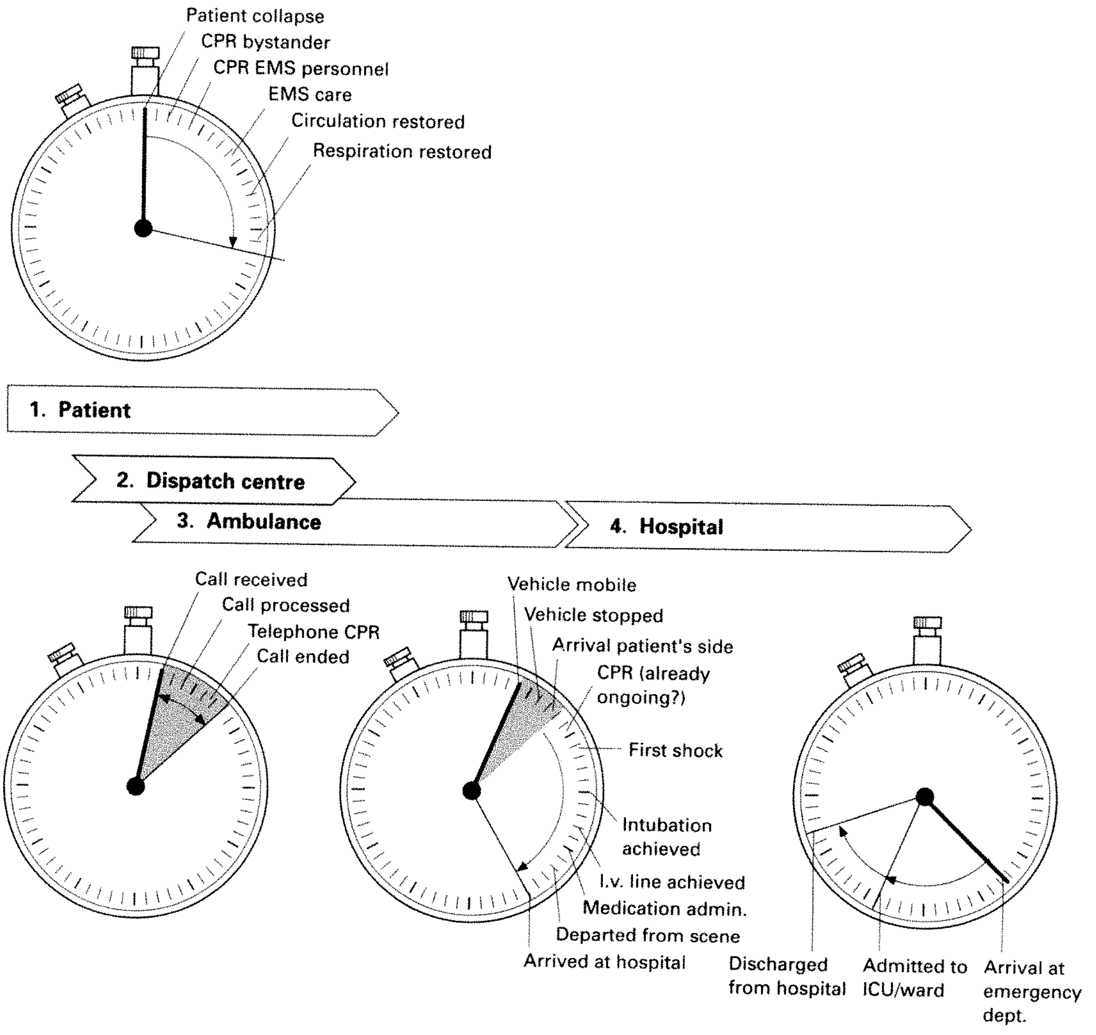

Figure 1 The four clocks of sudden cardiac arrest (reproduced from Chamberlain and colleagues[8] with permission).

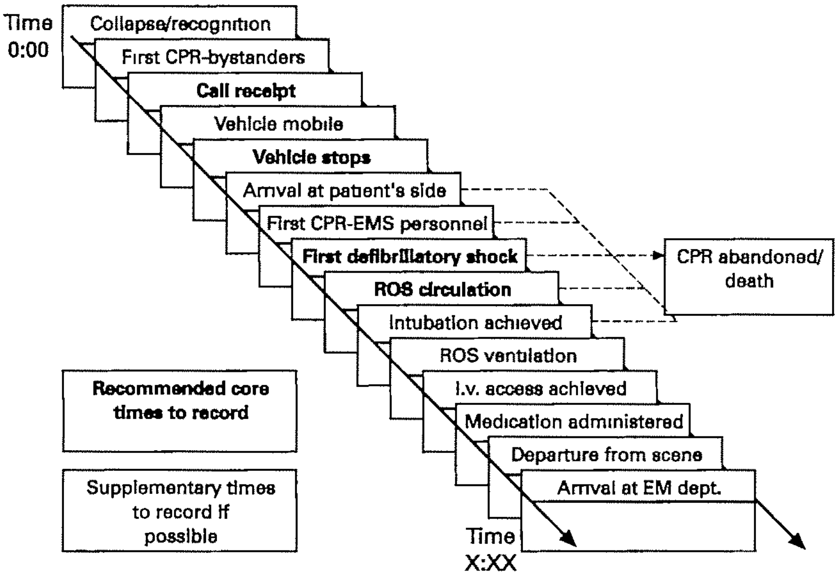

Figure 2 Events associated with out-of-hospital cardiac arrest resuscitation attempts (reproduced from Chamberlain and colleagues[8] with permission).

Collapse to cardiac arrest–recognition interval

Collapse witnessed/recognized.

EMS called
Time of call receipt
BLS starts by bystander
Call processed
First vehicle mobile
Call–response interval.

Arrival of the first ambulance at the scene
Call–arrival interval
Arrival of the first team at the patient side
Call to patient contact interval
BLS continued by professional responders

Arrival of the second tier at the scene
Arrival of the second tier at the patient side.

ALS starts with defibrillation, intubation, i.v. access, medication.
Call to defibrillation–intubation–medication interval

Time of restoration of spontaneous circulation (ROSC)
Call to ROSC interval
Time of departure from the scene
Scene interval
Time of arrival at the emergency department (ED)
Call to ED interval
= Total pre-hospital interval (or time)

Before the introduction of the Utstein template, many events and intervals were frequently not recorded or were confused (e.g. the call–arrival interval was almost always used synonymously with the call to patient contact interval, although the difference between the two intervals may be in the order of 5 min).[7]

Structure of the EMS system

The structure of the emergency medical services (EMS) system is of crucial importance. The initial intervals are determined by the structure, quality and efficiency of the EMS. The template provides an accurate description and classification of the EMS response based on core and supplementary data collected at the dispatch centre (who does what, how and when, and how well?).

Epidemiological and outcome data

In addition to developing a template for uniform reporting of events and intervals it was considered essential to evolve a template for obtaining data on survival, survival rates and quality of life after survival. The template allows description of the population served by the EMS, including information on age, sex, education, socioeconomic status, total number of deaths, incidence of ischaemic heart disease and deaths per 100 000 of the local population (only rarely available). Also included are definitions of confirmed arrest and recommendations as to when resuscitation should or should not be attempted, replacing traditionally used terms such as do not resuscitate (DNR) with do not attempt to resuscitate (DNAR).

Differentiation between initial VF/VT or asystole is important with regard to outcome. The rhythms of electromechanical dissociation (EMD) or pulseless electrical activity (PEA) are still only poorly defined.[9]

A large number of the terms referred to above can be used to describe outcome, for example ROSC at the scene, during transport or on admission, survival to admission to the ICU, general ward, rehabilitation unit or discharge from hospital, survival after cardiac arrest for 6 months, 1 yr, etc. However, information on survival rates alone is inadequate because it does not describe the quality of life after survival. To provide additional data on quality of life at discharge or after survival for 1 yr, the Utstein template recommends the use of the Glasgow–Pittsburgh outcome categories, overall performance categories (OPC) and cerebral performance categories (CPC), although other systems may be used for this purpose.

Forms for uniform reporting of data from out-of-hospital cardiac arrest

To complement the Utstein meeting, a form for uniform reporting of data from out-of-hospital and in-hospital cardiac arrest[13] was prepared and published by a working group consisting of representatives of the ERC, EAA and the Belgian Society for Emergency and Disaster Medicine. The form facilitates the use of the Utstein template.

Publication policy

The Utstein template recommends that publications on CPR should follow the Utstein style to overcome the present confusion arising from the lack of a uniform terminology and general agreement on data to be recorded.

Comment

Several prospective, randomized, comparative, controlled studies in the pre-hospital setting have been performed according to the Utstein style. Most investigations were designed to evaluate the efficacy of new methods of CPR compared with traditional CPR (ACD–CPR, Vest–CPR, etc).

Although it is becoming increasingly apparent that the Utstein template offers an excellent description of the course of resuscitation, from occurrence of cardiac arrest to survival or death under various conditions, there is still a lack of accurate information on the underlying disease. The Utstein template does not differentiate between cardiac arrest caused by electrophysiological disturbances occurring in a young patient or an extensive myocardial infarction in an older patient with coronary artery disease and major myocardial dysfunction.

While the Utstein template provides information on survival and quality of pre-hospital and in-hospital care for these patients, it does not permit conclusions to be drawn on the overall efficacy of the selected treatment. While the use of a resuscitative technique or drug may be highly effective in a young patient with an electrophysiological disorder, it may prove ineffective in an older patient with a malfunctioning myocardium.

UNIFORM REPORTING OF PAEDIATRIC ADVANCED LIFE SUPPORT: THE PAEDIATRIC UTSTEIN STYLE[32]

This "statement for health professionals" was developed by a task force from the American Academy of Pediatrics, American Heart Association and European Resuscitation Council who found that the original Utstein template for reporting adult out-of-hospital data was unsuitable for paediatric use.

Data are presented on the high morbidity, mortality and poor outcome rates in infants and children requiring resuscitation and emphasize the need for guidelines based on scientific evidence, although the latter are only rarely available.

Glossary of terms/dictionary of terms

The paediatric Utstein template, in common with the Utstein template for adults, addresses the problem of a uniform terminology in the "dictionary of key terms" and continues with recommendations for core and supplementary data.

In addition to existing definitions for resuscitation, EMS, cardiac arrest and respiratory arrest, the paediatric Utstein template introduces the term "respiratory compromise" to define ineffective breathing requiring assisted ventilation in infants and children at risk of developing cardiac arrest after respiratory insufficiency.

"Bradycardia/poor perfusion" requiring basic CPR is another term which is different from the adult template. It applies to infants and children with organized cardiac electrical activity but with a low output and low perfusion, usually with heart rates less than 60 beat min^{-1}.

The paediatric template also distinguishes between sustained (>20 min) and intermittent (<20 min) return of spontaneous circulation (ROSC) and introduces the term "return of spontaneous ventilation" (ROSV).

The template includes "times and time intervals", but creates an interval not included in the adult template, the "start–stop CPR interval", that is the time from initiation of CPR to either ROSC or termination of efforts.

With a view to outcome, the paediatric template defines the return to pre-event conditions as the main goal of all resuscitative attempts. Further emphasis is placed on the importance of investigating efficiency and effectiveness. Of the available systems for measuring quality of outcome, only a modified version of the Glasgow–Pittsburgh outcome categories, with the added category "mild disability group", is recommended for measuring the quality of outcome in infants and children. Although factors such as OPC, CPC and length of ICU stay are considered in the "paediatric risk of mortality score", it fails to record the infant's or child's pre-event conditions. Another, although not yet validated, criterion for measuring quality of outcome may be "time to awakening or return to consciousness".

Reporting of ALS data

In accordance with the adult template, a template for uniform reporting of advanced life support (ALS) has been developed for infants and children to obtain data on epidemiology, aetiology, location of event, etc.

Patient data

Various denominators and numerators have been recommended to calculate the incidence of a wide variety of criteria (fig. 3). The following age groups have been established: 0–12 months, 1–4 yr, 5–12 yr and 13–18 yr. The patient characteristics section of the template discusses the division of the paediatric population into children and adolescents,

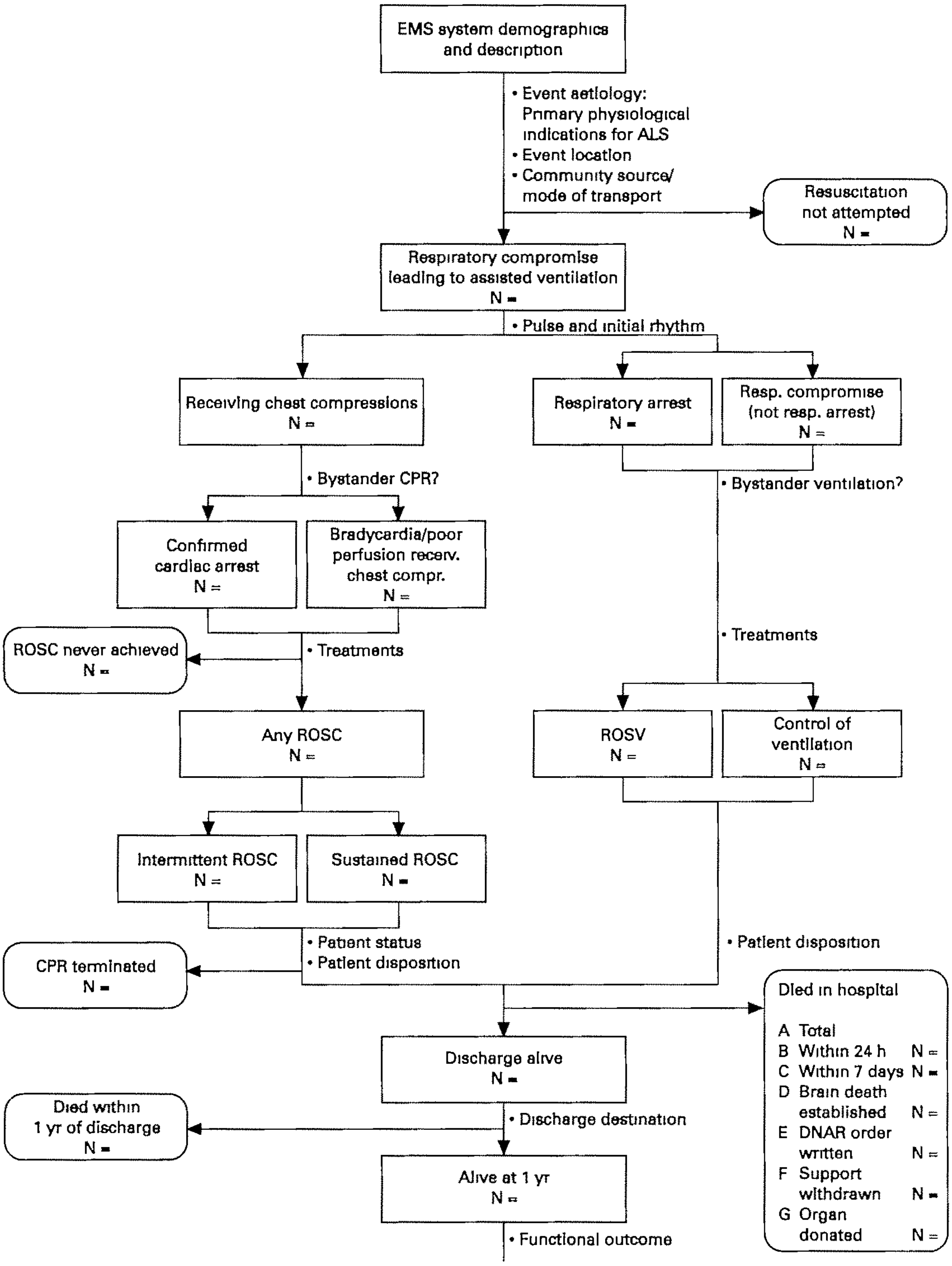
EMS system demographics and description
• Event aetiology: Primary physiological indications for ALS
• Event location
• Community source/ mode of transport
Resuscitation not attempted N =
Respiratory compromise leading to assisted ventilation N =
• Pulse and initial rhythm
Receiving chest compressions N =
Respiratory arrest N =
Resp. compromise (not resp. arrest) N =
• Bystander CPR?
• Bystander ventilation?
Confirmed cardiac arrest N =
Bradycardia/poor perfusion receiv. chest compr. N =
ROSC never achieved N =
• Treatments
• Treatments
Any ROSC N =
ROSV N =
Control of ventilation N =
Intermittent ROSC N =
Sustained ROSC N =
• Patient status
• Patient disposition
• Patient disposition
CPR terminated N =
Died in hospital
A Total
B Within 24 h N =
C Within 7 days N =
D Brain death established N =
E DNAR order written N =
F Support withdrawn N =
G Organ donated N =
Discharge alive N =
Died within 1 yr of discharge N =
• Discharge destination
Alive at 1 yr N =
• Functional outcome

Figure 3 Paediatric Utstein style template (reproduced from Zaritzki and colleagues[32] with permission).

recommending the use of the term "child" for individuals up to 13 yr of age and "adolescent" for those aged 13–18 yr. For patient data purposes, anyone less than 19 yr of age is included in the paediatric population.

Influence of the EMS system

The impact of an EMS system on the outcome in paediatric age groups has never been documented sufficiently. This may be because in contrast with adult populations with a high incidence of VF/VT there is an absence of a predominant diagnosis in this age group. Few investigations have been performed on events such as near-drowning or trauma, for example, to provide adequate data to determine the influence of the EMS on paediatric outcome. It was therefore considered essential to include the same EMS system data as in the adult Utstein template.

Hospitals

In contrast with the adult template, the paediatric template recommends a description of the hospital to which the infant or child is transferred (children's or general hospital, number of beds, classification, trauma level, ED, number of ED patients per year, etc). Unfortunately, hospital data have not been included in either the initial or updated version of the Utstein I template. However, in addition to quality of primary care provided by the EMS, quality of care in the hospital itself may influence outcome decisively. In common with the description of the EMS, the description of the hospital should include data on quality of hospital personnel, level of training, personnel responsible for resuscitation, intensive care units, emergency departments, etc.

Events, primary care, patient status at different levels

The paediatric template provides further opportunities for the description of aetiology, location, type of cardiac arrest and quality of initial care. In addition to the recommendations in the adult template for reporting aetiology, the inclusion of information as to whether or not the event resulted from respiratory or circulatory compromise or was caused by cardiorespiratory failure, has been suggested. In addition, classification of the underlying disease according to ICD 9 has been recommended. Concomitant diseases or conditions which may influence outcome should also be reported. It should be stated if the event occurred at home, on the street, at school or work, or in a transport vehicle. Events occurring during inter- or in-hospital transfer or in the ICU should be recorded separately.

Other items which are reported slightly differently in the paediatric template include the pre-event clinical status, clinical status before arrival of the first EMS provider, pre-event monitoring, witnessing of the event, "resuscitation not attempted" information and initial rhythm and pulse.

Diagnosis of supraventricular tachycardia (SVT) in infants and children requires a heart rate of more than 200 beat min^{-1}, which may be difficult to differentiate from sinus tachycardia. The diagnosis of bradycardia requires a heart rate of less than 60 beat min^{-1}.

The level of response to stimulation is assessed by the AVPU scale (*a*lert and responsive, responsive only to *v*erbal stimulation, responsive only to *p*ainful stimulation and *u*nresponsive).

As with the adult template, deaths in hospital are categorized as follows: deaths within 24 h or deaths between 1 and 7 days, related to the total number of deaths. For survivors, the discharge location (home, etc) is recorded. Outcome is defined according to paediatric cerebral and overall categories at all times after discharge.

Unresolved problems include the age at which a child becomes an adolescent or adult (14 or 16 yr?), definition of trauma centres, aetiology, pre-existing morbidity, neurological function after the event, neurological outcome, etc.

Refinements of the document will be published in updated versions of the statement and comments are invited from those involved in paediatric resuscitation.

UNIFORM REPORTING OF DATA FROM IN-HOSPITAL RESUSCITATION: THE IN-HOSPITAL UTSTEIN STYLE[9]

As with the out-of-hospital situation, the efficiency of in-hospital-resuscitation is not based on solid scientific evidence. Data available from retrospective reviews and from the prospective British Resuscitation Study (BRESUS) demonstrate that at 24 h after in-hospital cardiac arrest, survival ranges from 3 to 59%, and from 3 to 27% at discharge.[31] However, this information is influenced by many variations in definitions and procedures of reporting.

The in-hospital cardiac arrest template presents definitions of, for example, what precisely is a cardiac arrest (cessation of cardiac mechanical activity confirmed by the absence of a detectable pulse, unresponsiveness and apnoea or agonal gasping). In contrast with the out-of-hospital situation, however, a hospital patient may be unresponsive or apnoeic because of controlled sedation or anaesthesia. In addition, the co-morbidity rate is higher in in-hospital than in out-of-hospital patients.

Four in-hospital Utstein variables (hospital, patient, arrest and outcome factors) influencing outcome after in-hospital cardiac arrest have been identified in the Utstein template (fig. 4).

Patient variables include age, sex, race, socio-economic status, reasons for admission, pre-arrest and co-morbid conditions, severity estimates, ALS interventions in progress at the time of arrest, previous arrests, witnessed or unwitnessed arrests, and location of events.

The following age groups have been identified (differing slightly from the paediatric template): infancy (0–12 months); childhood (1<3, 3–<8, 8<14 and 14<20 yr); adulthood, with subdivisions into 5-yr periods (20<25 yr, etc).

As recommended in the other Utstein templates, pre-arrest capacities should be described according to the Glasgow–Pittsburgh outcome categories, including CPC and OPC (or the paediatric versions).

The definition of co-morbidity is considerably more difficult because the ICD 9 and ICD 9-CM are not used uniformly. Co-morbidity indices may be useful, although only one has thus far been developed for in-hospital purposes.

The severity of a medical condition can be described using APACHE scores for ICU patients, the pre-arrest morbidity score (PAM) or TISS. However, all of these systems are known to be flawed in some respects. Arrest variables comprise rhythms, interventions performed, and event times and intervals.

Event times and intervals are comparable with those in Utstein I but there are some subtle differences. The intervals shown below have been identified as suitable for inter-and intra-hospital comparisons.

Intervals from: cardiac arrest to start of CPR; cardiac arrest to first defibrillation; cardiac arrest to advanced airway management; and cardiac arrest to first administration of medication.

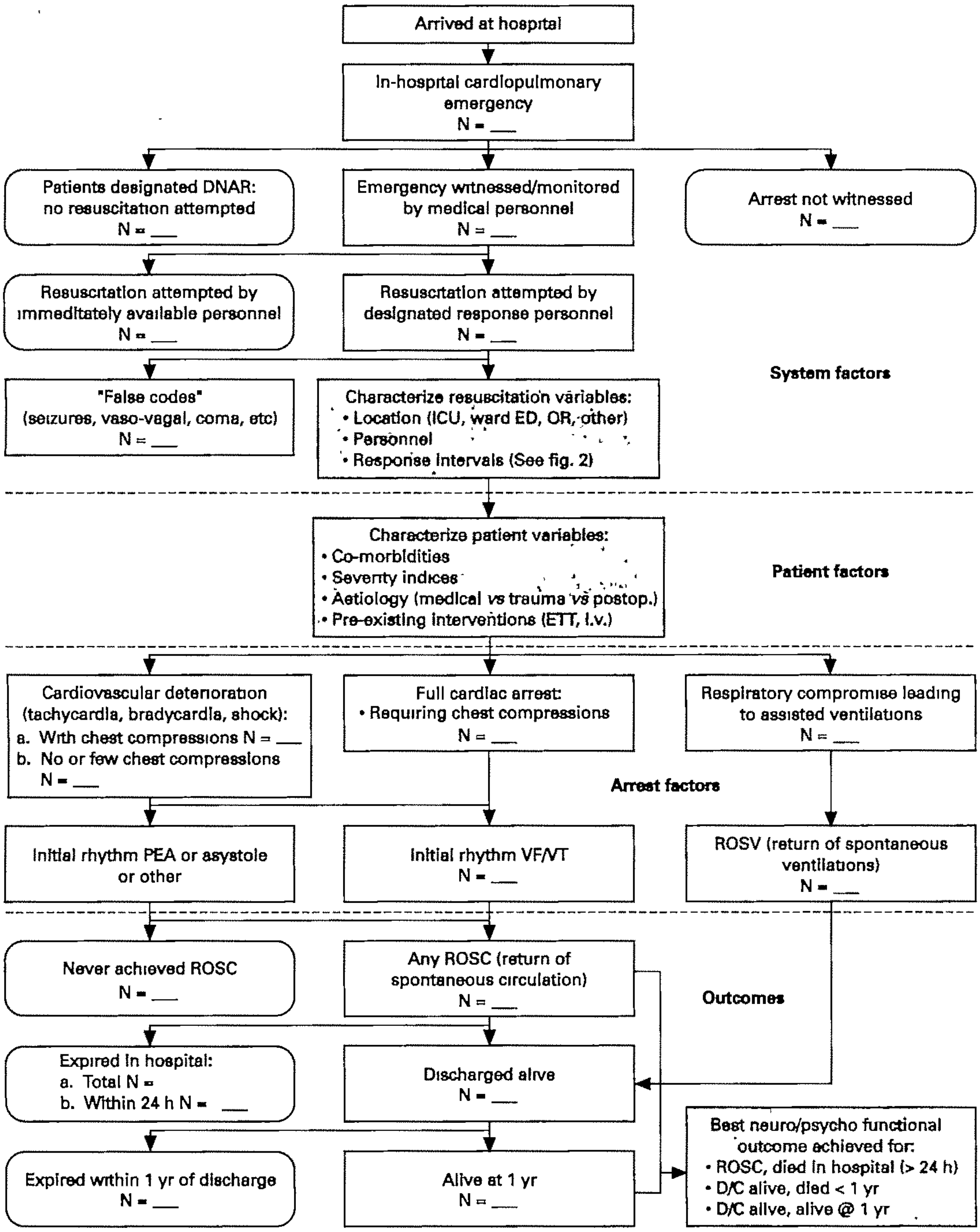
Arrived at hospital
In-hospital cardiopulmonary emergency N = __
Patients designated DNAR: no resuscitation attempted N = __
Emergency witnessed/monitored by medical personnel N = __
Arrest not witnessed N = __
Resuscitation attempted by immeditately available personnel N = __
Resuscitation attempted by designated response personnel N = __
System factors
"False codes" (seizures, vaso-vagal, coma, etc) N = __
Characterize resuscitation variables:
• Location (ICU, ward ED, OR, other)
• Personnel
• Response intervals (See fig. 2)
Characterize patient variables:
• Co-morbidities
• Severity indices
• Aetiology (medical vs trauma vs postop.)
• Pre-existing interventions (ETT, i.v.)
Patient factors
Cardiovascular deterioration (tachycardia, bradycardia, shock):
a. With chest compressions N = __
b. No or few chest compressions N = __
Full cardiac arrest: • Requiring chest compressions N = __
Respiratory compromise leading to assisted ventilations N = __
Arrest factors
Initial rhythm PEA or asystole or other
Initial rhythm VF/VT N = __
ROSV (return of spontaneous ventilations) N = __
Never achieved ROSC N = __
Any ROSC (return of spontaneous circulation) N = __
Outcomes
Expired in hospital:
a. Total N =
b. Within 24 h N = __
Discharged alive N = __
Best neuro/psycho functional outcome achieved for:
• ROSC, died in hospital (> 24 h)
• D/C alive, died < 1 yr
• D/C alive, alive @ 1 yr
Expired within 1 yr of discharge N = __
Alive at 1 yr N = __

Figure 4 In-hospital Utstein style template (reproduced from Chamberlain and colleagues[9] with permission).

Outcome variables include: survival (immediate, short-term and long-term); and quality of life after survival. The quality of life should be assessed using the Glasgow coma score, the Glasgow–Pittsburgh outcome categories leading to the CPC and OPC. The OPC and CPC should be recorded at discharge, and at 6-month and 1-yr intervals. Other recommended outcome criteria are length of hospital stay and costs per survivor.

Hospital variables did not allow accurate categorization, but the different variables are listed in appendix I of this template.

The final section of the template describes the procedure for completing the form (comparable with other templates). Examples refer to:

- Population served (numerators and denominators)
- Explanations of the definitions of a cardiac arrest
- Number of DNAR
- Attempted in-hospital resuscitations (defibrillations, compressions only, airway interventions, combinations)
- False arrests
- Non VF/VT rhythms (see also Utstein I)
- ROSC (intermittent and sustained≥20 min)
  —never achieved ROSC
  —death in hospital (<20 min, >20 min to <24 h, >24 h)
- Re-attempts/re-arrests
- DNAR, support withdrawn, brain dead, organ donation.

Survival figures

One of the most important questions is how should survival be best reported and at what times? The recommendations of the BRESUS study have been adopted.

- Percentage survival from arrest to at least 24 h
- Percentage survival from >24 h to 1 yr
- Percentage survival from arrest to discharge
- Percentage survival from discharge to 1 yr
- Percentage survival from arrest to 1 yr.

However, it is not sufficient that resuscitation is initiated and performed as early as possible, it must also be carried out according to specific quality standards. This gives rise to the question, how is the quality of performance to be rated ?

Apart from haemodynamic criteria (difficult to measure) or pulse oximetry, end-tidal carbon dioxide concentration appears to be the most useful criterion. The pulse check merely confirms whether or not a pulse is present and in many cases may be misleading, as has been shown by our group in a human model[18] designed to simulate cardiac arrest during cardiopulmonary bypass.

The final chapter of the in-hospital template refers to ethical issues in general, informed consent and to the futility of CPR in certain circumstances.

Appendices to the template summarize the following items: data elements; a checklist of information and figures of the template itself, and a standard report form.

With the availability of the widely distributed in-hospital template, it is important to use this template as frequently as possible to determine its value compared with the out-of-hospital version.

Uniform reporting of laboratory CPR research[10 21 23]

"Modern cardiopulmonary resuscitation (CPR) research depends on the use of animal models that are designed to simulate cardiac arrest in humans."[22] This is the introductory statement and guiding principle of the "animal research Utstein style template" which was developed at a conference in Chicago in 1994. Only a few days after the Chicago meeting the proposed guidelines for CPR research were presented and discussed at the Second Congress of the ERC—Resuscitation 94—in Mainz, Germany, with the purpose of "setting guidelines for CPR research".

Consistent with the other Utstein documents, this template begins with a glossary of key terms.

Glossary of key terms

Baseline conditions are described as the "physiological conditions after the animal has been instrumented" but before induction of cardiac arrest. Therefore, these baseline values do not represent true physiological conditions.

Cardiac arrest in an animal model allows a more precise description than cardiac arrest in humans (i.e. VF or asystole, loss of intra-arterial pressure (<25 mm Hg in the aorta), etc).

Ventilation should be reported with consideration of at least two of the following variables: ventilatory frequency, tidal volume and minute ventilation.

Standard CPR. Although this has been established for human CPR, a standard cannot be set for animal CPR because of the wide variety of species, with their differences in size, anatomical configurations, physiology, etc. Thus even though the term "standard CPR" should not be used for CPR in animals, the technique used is to be described meticulously.

Active decompression. Any device used for this technique should be described.

Blood flow. Any method used for measurement of blood flow or regional specific blood flow should be documented.

ROSC. In view of the fact that at least 11 different definitions of ROSC have been proposed, the conference recommended the following definition of ROSC: an aortic arterial pressure of at least 60 mm Hg for at least 10 consecutive minutes (mean, median and confidence intervals).

Survival. This should comprise a minimum of 24 h after resuscitation, including a description of neurological status, multisystem failure, etc.

Intensive care should document any drugs given, at what dosage and how frequently, in addition to any other technical assistance used (defibrillation, assist devices, ventilatory support, etc.)

Intervals and times do not differ from Utstein I.

Experimental events and intervals should be recorded.

Non-intervention intervals. As this is one of the most important intervals and may in itself decide survival or death, it must be described clearly (not in terms of "down time", for example).

An "experimental time line" should provide a graphic description of the above factors (fig. 5).

Induction of cardiac arrest. This is defined as the moment of no blood flow. This cannot be ascertained in cases of asphyxia and exsanguination. In the latter, a pre-selected critical value should serve as the target (e.g. <25 mm Hg)

Compression and release. Phase measurements: during CPR, systolic or diastolic periods cease to exist. Pressures during compression and release should therefore be described.

Defibrillation attempt or rescue shock refer to defibrillation during an "experimentally induced episode of VF". Number of shocks, timing and energy should be reported.

Coronary or myocardial perfusion pressure. Coronary perfusion pressure is generally calculated on the basis of simultaneous difference between aortic and right atrial pressure during diastole or the release phase. The method of calculation should be described.

THE ENTIRE TEMPLATE IS DIVIDED INTO NINE SECTIONS

Study design

Consistent with the Utstein I template, it is recommended to distinguish between "essential" or "core

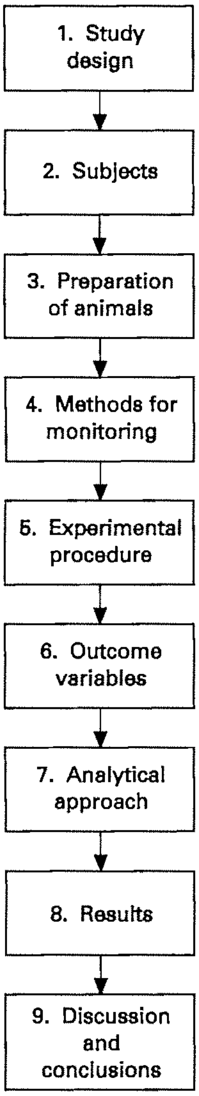
1. Study design
2. Subjects
3. Preparation of animals
4. Methods for monitoring
5. Experimental procedure
6. Outcome variables
7. Analytical approach
8. Results
9. Discussion and conclusions

Figure 5 Reporting template, listing features to describe when reporting laboratory studies on resuscitation (reproduced from Idris and colleagues[22] with permission).

data" and "supportive, useful or desirable data". A prospective study with concurrent control groups is suggested as the optimum study design. The type of blinding needs to be documented where applicable.

Subjects

Physiological conditions need to be targeted for all species and the absence of infections or other diseases. The source of the animals should be reported, and age range, sex, etc. (rats, dogs, swine).

Preparation

Pre-anaesthesia conditions and premedication with sedatives or analgesics, or both, should be reported, and anaesthetic techniques should be described, including doses of drugs used. Maintaining a period of stabilization is essential.

Monitoring

Baseline monitoring includes: heart rate, cardiac output, coronary perfusion pressure; arterial pressure (arterial, mean and cyclic); central venous/right atrial vascular resistances; end-tidal carbon dioxide, arterial and central venous blood-gas analysis and electrolyte concentrations; oesophageal, rectal, PA, VC, bladder or tympanic temperature.

Experimental procedure

An experimental procedure covers the period from induction of cardiac arrest to ROSC or comparable variables of outcome. It cannot be emphasized enough that procedures need to be clinically relevant, for example in VF the non-intervention interval needs to be as close to pre-hospital human conditions as possible (3, 5, 10 min?).

Maintaining minute ventilation constant requires specific types of ventilators; inspired oxygen concentration needs to be documented at regular intervals together with other ventilation variables. Furthermore, information should be provided on synchronization of compression and ventilation. Haemodynamic and blood-gas monitoring, pulse oximetry and end-tidal carbon dioxide measurements should be recorded at regular intervals.

The method of inducing cardiac arrest should be described, in addition to the type of defibrillator used to terminate VF. Energy levels, number of shock attempts and additional medication should be recorded.

Blood flow measurements and changes in blood flow are important factors that need to be recorded (implantable flow probes, microsphere techniques, catheter based techniques).

Outcome variables

In addition to ROSC and the other variables outlined above, short-term and long-term survival are recommended outcome variables. GPCS, OPC, neurological deficit scores and histopathological damage scores have been used to evaluate outcome. It is nevertheless important to bear in mind the limitations of these variables, particularly when applied to animal studies. Cerebral outcome may be calculated on the basis of EEG patterns, EVP patterns and morphological brain investigations.

Statistical methods and publication policies of the respective journals are the topics of the final three sections.

Disaster medical response research: a template in the Utstein style

Although this template is only loosely related to resuscitation, it should be mentioned briefly because it refers to the term Utstein style. In the introductory section of this document the authors draw attention to the fact that there is no uniform methodology for the conduct and reporting of research in disaster responses.[30] In 1995 a meeting was convened at the Utstein Abbey with the purpose of developing a methodology for the conduct and reporting of research in disasters, proceeding in the same manner as for the development of

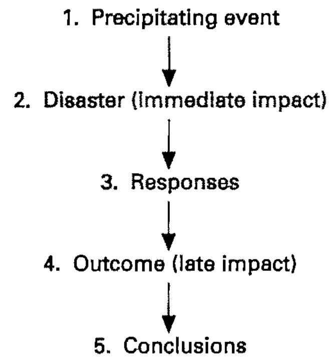

Figure 6 General template used for descriptive evaluations of the medical responses to a disaster (reproduced from Sundness and colleagues[30] with permission).

templates for cardiac arrest and resuscitation in adults, infants and animals.

The first chapter of the document attempts to define "What is a disaster?" and specifically "What is a medical disaster?" (fig. 6) before discussing the objectives of a medical disaster response and methods used for medical disaster research. The working group proposed a template for conducting and reporting research in disaster response.

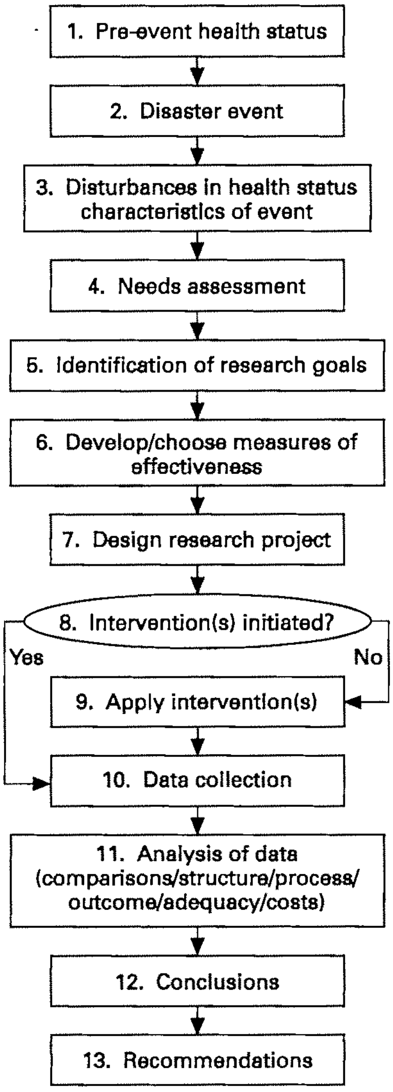
1. Pre-event health status
2. Disaster event
3. Disturbances in health status characteristics of event
4. Needs assessment
5. Identification of research goals
6. Develop/choose measures of effectiveness
7. Design research project
8. Intervention(s) initiated?
Yes
No
9. Apply intervention(s)
10. Data collection
11. Analysis of data (comparisons/structure/process/outcome/adequacy/costs)
12. Conclusions
13. Recommendations

Figure 7 Disaster medicine research template (reproduced from Sundness and colleagues[30] with permission).

The disaster medicine research template provides definitions for: pre-event health status, disaster event, disturbances in health status, characteristics of events, identification of research goals, measures of effectiveness, interventions, data collection, analysis of data, etc. Each of these definitions includes examples of disaster events subdivided according to type, that is natural, human or technological origin, and the character of the onset of the event (sudden, gradual or delayed impact), secondary effects, time and location, scope or magnitude, total population affected, number of refugees and displaced persons, major causes of injury, source, timing and scope of medical assistance, response time (fig. 7), character of responses, public health, early warnings, etc.

Although this template is the result of a discussion by a group of experts, it has never been tested in the field. The first version of the template has been published in *Prehospital and Disaster Medicine*.[30]

The effectiveness of the template must await testing.

Uniform reporting of data from resuscitation after trauma

Another issue in urgent need of standardization is the pre-hospital care of the trauma patient. At present, trauma patients are treated either via the scoop-and-run or stay-and-play approach[25] by either ambulancemen, emergency medical technicians, nurses/paramedics or emergency physicians, or a combination of these, and transferred to level I–III trauma centres or to hospitals providing different levels of treatment, although they are not recognized as trauma centres.

In 1990 Jones and Brenneis[24] noted that trauma studies could not be compared because of the lack of a prospective, randomized, controlled study design. Similar conclusions were drawn by Spaite and colleagues in 1995[29] emphasizing that the efficiency and quality of trauma care in terms of outcome and quality of life requires the availability of uniform terminology. This terminology has subsequently been developed in the "Utstein style".

The International Trauma Anaesthesia Critical Care Society (ITACCS) and the European Society for Emergency Medicine have recently formed a working group consisting of anaesthetists, trauma surgeons, epidemiologists and emergency physicians. Within the next few months the group expects to complete work on a template for uniform reporting of data after trauma.[17]

Several aspects of the Utstein I template can be used in the trauma template. These include descriptions and terminology defining the emergency medical system, times and intervals. Definitions of major, moderate and minor trauma, multiple injuries, polytrauma, the standard of care in terms of basic trauma life support, advanced trauma life support, scoring systems for the assessment of the patient's general condition and injuries need to be re-designed. The term "standard of trauma care"

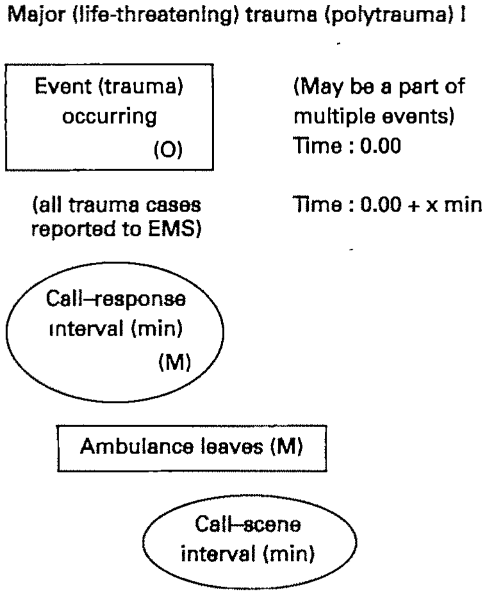
Major (life-threatening) trauma (polytrauma) !
Event (trauma) occurring (O)
(May be a part of multiple events) Time : 0.00
(all trauma cases reported to EMS)
Time : 0.00 + x min
Call–response interval (min) (M)
Ambulance leaves (M)
Call–scene interval (min)

Figure 8 Draft template for uniform reporting of data after trauma (reproduced from Dick[17]).

can no longer be accepted as valid in the absence of scientific proof demonstrating that the methods comprising this standard are valid. Certain aspects of care require scientific evaluation, such as fluid resuscitation, airway management and brain protection (fig. 8).[5 6 16 27]

In common with previous Utstein templates, the trauma template needs to define the quality of life after survival following severe trauma (for example 30 days after injury) and the criteria to be used for this purpose (Glasgow coma outcome category, including overall performance categories and cerebral performance categories, major trauma outcome study system, etc).

Summary[12]

The concept of uniform reporting of data in resuscitation has demonstrated its potential value in pre-hospital and in-hospital cardiac arrest in adults, infants and children, in laboratory research, in disaster research and, hopefully, also in trauma care and research.

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British Journal of Anaesthesia 1997; **79**: 253–259

Ethical aspects of resuscitation

M. MOHR AND D. KETTLER

The current technique of cardiopulmonary resuscitation (CPR), applying expired air ventilation and closed chest cardiac massage, was developed at the beginning of the 1960s. It was an easy-to-learn method which was soon disseminated: "Anyone, anywhere, can now initiate cardiac resuscitative procedures. All that is needed are two hands".[35] Originally developed for the treatment of sudden and unexpected cardiac arrest in supposedly healthy persons, after the first successes this treatment was extended to cardiopulmonary arrest of any origin. CPR is now considered a routine emergency treatment but the reflex-like initiation of CPR has also entailed criticism. In 1985 an editorial in the *Journal of the American Medical Association* stated: "In some way we have wandered from treating sudden unexpected death to practising universal resuscitation".[28] Despite all attempts and modern measures, the majority of resuscitative efforts remain unsuccessful, and only a small minority of patients are returned to their previous health status. Therefore, the appropriateness of CPR procedures has been questioned, especially with respect to individual outcome and patient preference.[3,12,36]

Ethical reasoning in resuscitation

It may be argued that the nature of a resuscitation attempt, demanding immediate and often irreversible interventions, makes ethical deliberation impossible. Even though CPR is an emergency measure, its practice—just as that of any other medical procedure—must be guided by general ethical principles. Beauchamp and Childress have listed four aspects of bioethics to be considered[7]: (1) ethical theories; (2) principles; (3) rules; and (4) particular judgements and actions.

The decision to start CPR is based on a medical judgement that a person is suffering from circulatory arrest. The decision to resuscitate is justified by the moral rule that the victim of a cardiac arrest has the right to be given the opportunity to survive and to receive CPR. The obligation to give aid also belongs to the generally accepted moral rules.

Moral rules are based on ethical principles. Beauchamp and Childress suggest four principles for acceptance as action guides in medicine[7]:

- the principle of beneficence;
- the principle of nonmaleficence;
- the principle of respect for autonomy;
- the principle of justice.

The precise distinction between rules and principles is controversial. Principles are characterized as general and fundamental, and serve to justify moral rules.[7] Rules are related to specific contexts and more restricted in scope. Principles are conceived as binding, but not absolutely binding. This permits each basic principle to have weight without the determination of a ranking.[7] Which principle applies in a case of conflict depends on the unique emergency situation.

Ethical theories represent the integration of principles and rules, depending on individual beliefs and customs.[7] Diverse scientific, metaphysical and religious beliefs may determine the interpretation of a situation and the ethical theory. Ethical theories may serve to justify the principle, the rule and the particular judgement, but they are abstract in nature and may be inapplicable in clinical practice. How might the ethical principles be taken into consideration in clinical resuscitation practice and what might be their consequences?

BENEFICENCE

The principle of beneficence encompasses the fundamental goals of medicine, which are[45]:

- preservation of life;
- restoration of health;
- relief of suffering;
- restoration or maintenance of function.

Modern resuscitation procedures, training of lay persons in basic life support and expansion of effective emergency cardiac care systems have saved many victims from pre-hospital and in-hospital sudden death. The success and beneficence of standardized resuscitation procedures is emphasized by the American Heart Association at the beginning of the Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiac Care: "In the past 30 years, since the introduction of modern

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Key words
Ethics Heart, resuscitation. Complications, cardiac arrest. Medico-legal, consent.

MICHAEL MOHR, MD, DIETRICH KETTLER, FRCA, Department of Anaesthesiology, Critical Care and Emergency Medicine, University of Goettingen, Robert-Koch-Str. 40, D-37075 Goettingen, Germany.

techniques of CPR, there have been dramatic advances in emergency cardiac care of victims with profound circulatory collapse and cardiac arrest. These techniques have restored the lives of many people when breathing has ceased and the heart has stopped beating".[2] Attempts have been made to identify factors indicating a favourable prognosis after resuscitation in the pre-hospital setting in order to provide criteria to facilitate the decision whether to initiate, withhold or discontinue resuscitation attempts.[13 25] The highest survival rate after cardiac arrest occurs when the collapse is observed, when circulatory arrest is caused primarily by cardiac failure with ventricular fibrillation, when lay persons have already applied bystander resuscitation and when professional support arrives at the scene within a very short time.[25]

However, the overall long-term survival rate of 70% reported in the historical article by Kouwenhoven, Jude and Knickerbocker[35] has not been reproduced in more recent investigations. Comparison of different publications on outcome of resuscitation attempts shows an initial resuscitation success in terms of restoration of the circulation of up to 50% (table 1). The proportion of patients who survive after a cardiac arrest to discharge from hospital ranges from 0 to 20%. The results of studies vary, depending on differences in cause and location of circulatory arrest (in-hospital *vs* pre-hospital) and the varying effectiveness of emergency care.

Interviews with survivors of cardiac arrest show that resuscitation and survival are evaluated positively by the majority of patients. Bedell and colleagues[10] interviewed 38 mentally competent survivors of circulatory arrest at the time of discharge from hospital; 21 (55%) said that they would choose to be resuscitated in the future. Follow-up of 28 survivors of cardiac arrest, interviewed 19–43 months after hospital discharge, showed that 89% felt positive about the resuscitation, and 67% would consent to another resuscitation attempt.[42]

NONMALEVOLENCE

Nonmaleficence incorporates the principle of "above all do not harm, or *primum non nocere*".[1] Nonmaleficence implies avoiding anything that might have negative consequences, whereas beneficence means the performance of positive acts to promote good.[7]

In the event of circulatory arrest, the patient is in danger of dying within minutes. Any resuscitation attempt aims at averting death (maleficence) and saving life (beneficence). Can further damage be inflicted by a resuscitation attempt?

Resuscitative efforts are unsuccessful in the majority of cases. In at least in 50% of cardiac arrests, the action of the heart cannot be restored (table 1); another 30% die in hospital after successful restoration of the circulation. For these patients, resuscitation means an extension of the process of dying by hours or days, often without regaining consciousness and accompanied by the concomitants of intensive care treatment, such as tracheal intubation and artificial respiration. This means considerable suffering for the patient and relatives, and is a heavy burden for those involved, including the hospital staff. Of those who survive, approximately 20–50% suffer from neurological disabilities,[23] ranging from slight disturbances of cognitive functions to the "ultimate tragedy" of resuscitation[5] —severe hypoxic brain damage (persistent vegetative state).

Evaluation of survivors of cardiac arrest revealed a decrease in functional status caused by the fear of another cardiac arrest.[10] Others reported that 35% of survivors had a reduced capacity to perform activities in everyday life.[46] These disabilities often resulted in physical dependence on other people (nursing homes); only a small percentage were able to return to work. Altered social contacts were common after the cardiac arrest, with 42% of patients complaining of social isolation.[46]

High survival rates after cardiopulmonary arrest are the exception rather than the rule.[8] Centres reporting their results may indicate a particular interest in emergency cardiac care in these locations. Therefore, these centres might not be representative of all communities or hospitals. Overall survival rates in the USA have been estimated to be only 3–5%.[8]

CPR after trauma is associated with a very poor outcome, with a survival rate close to zero.[15 43] These discouraging results are independent of differences in patient selection and levels of trauma care. Even in physician-staffed pre-hospital trauma care systems, the chance of surviving a post-traumatic cardiac arrest is minimal. The poor results are very

Table 1 Outcome of pre-hospital and in-hospital cardiopulmonary resuscitation in the adult

				No. of CPR attempts	Initially successful (%)	Discharged alive (%)
Westfal[50]	New York	1996	Pre-hosp.	481	17.9	1.5
Schultz[44]	Washington	1996	In-hosp.	266	28.2	9.0
Gaul[27]	Vienna	1996	Pre-hosp.	249	43.8	10.8
Valentin[47]	Vienna	1995	In-hosp.	253	55.7	19.8
Wuerz[51]	Hershey	1995	Pre-hosp.	532	17.1	5.3
Kass[31]	Albany	1994	Pre-hosp.	599	32.2	6.0
Beuret[11]	Lausanne	1993	In-hosp.	181	29.8	12.7
Juchems[30]	Aschaffenburg	1993	In-hosp.	574	46.7	20.2
Kellermann[33]	Memphis	1993	Pre-hosp.	1068	29.0	8.0
Kettler[34]	Göttingen	1992	Pre-hosp.	429	43.1	17.9
Total			Pre-hosp.	3358	29.1	7.7
			In-hosp.	1274	42.2	16.7
				4632	32.7	10.2

disappointing considering the generally young age of the victims and the high expenditure which is often required for rescue operations associated with accidents.[15]

The poor survival rates after a traumatic cardiac arrest have lead to discussion of futility in resuscitation. Initiation of CPR is obviously not indicated when there are signs of death, such as post-mortem lividity, rigor mortis or decomposition. Nevertheless, even if these signs are absent, the efficacy of a resuscitation attempt may be in doubt and the aspect of futility has to be considered. For a treatment to be judged futile it must be ascertained that it has no benefit. The benefit of a treatment depends on the outcome of the intervention, the probability of that outcome and the patient's perception of that outcome.[21] There are some situations where efforts to resuscitate appear to be futile with regard to the expected physiological outcome. Unilateral decisions by physicians to withhold or terminate resuscitation based on a medical judgement of futility may be justified[2]:

- in conditions where scientific investigations have demonstrated the ineffectiveness of resuscitative efforts;
- in patients suffering cardiac arrest despite optimal treatment to maintain vital functions (e.g. in progressive cardiogenic shock);
- in patients where appropriate resuscitative efforts have been attempted without restoration of circulation.

These circumstances represent the recommendations of the 1992 American Heart Association conference panel on ethical issues in adult resuscitation. It was the consensus that futility should be strictly defined and that it should represent zero benefit.[21] Using the term futility more loosely involves value judgements which need to be discussed with the patient or his surrogate.[2]

PATIENT AUTONOMY

Physicians do not have the right to treat patients without their consent: *Voluntas aegroti suprema lex.* The right to consent or to refuse is based on the principle of respect for autonomy.[7] Physicians must obtain informed consent from patients before undertaking procedures. The following elements have been proposed as the components of informed consent[7]: (1) competence; (2) disclosure of information; (3) understanding of information; (4) voluntariness; and (5) authorization

The process of informed consent from a competent patient involves adequate disclosure and understanding of information concerning the consequences of the intervention and the potential alternatives so that a voluntary decision to authorize or refuse a medical procedure can be made. In bioethical contexts *competence* implies the ability to make a decision as to whether or not a therapeutic or diagnostic procedure should be undertaken.[7] The patient's decision should reflect rational considerations based on information given by the physician. The process of *disclosure* includes information on the nature of the disease, prognosis and risks and benefits of the various options. However, there seems to be a considerable lack of *understanding* by patients of the procedure of resuscitation and the prognostic implications. For example, it has been demonstrated that providing knowledge about CPR and survival rate can lead to a marked decrease in consent to resuscitation in the elderly.[39] A high percentage (41%) of ambulatory patients interviewed in a geriatric practice said they would opt for CPR if they had a cardiac arrest during an acute illness. In the case of cardiac arrest during a chronic illness (life expectancy less than 1 yr), the number of patients choosing CPR decreased considerably (11%). There was a further reduction in acceptance of resuscitation attempts after additional information was disclosed as to the probable rate of survival in both conditions: now only 22% would still opt for CPR during an acute illness, and only 5% of the elderly patients would choose to undergo CPR during a chronic disease. These results emphasize the essential need for prognostic information for the patient to make an informed decision concerning CPR.[39]

Patient's autonomy in resuscitation

Voluntariness means "being free to act", a vital precondition for autonomous *authorization* of a diagnostic or therapeutic intervention.[7] However, within seconds after cardiac arrest the patient loses consciousness, and thus his decision-making capacity. He is incapable of communicating his treatment preferences, or his right to accept or reject treatment. Thus the decision to perform CPR in sudden cardiac arrest is usually made without the patient's involvement. Consent to administer CPR is presumed. Physicians (and all others involved) have an obligation to serve as the patient's advocate by attempting to avoid undue harm. Such behaviour might be judged a "paternalistic" approach in medical practice, but we believe it should be considered primarily as an attempt to do what is assumed to be in the patient's best interests. Those who want to make an independent decision as to whether or not resuscitation attempts should be started must express their wishes in advance or through a surrogate.

Do-not-resuscitate orders

The patient's wish not to be resuscitated has been recognized as a potential criterion for withholding CPR.[2] Do-not-resuscitate (DNR) orders written by patients or their physicians have been established to provide a mechanism for withholding specific resuscitative therapies in the event of cardiac arrest. DNR orders mean that no measures are undertaken to restore spontaneous cardiac rhythm and respiration.[32]

Patients may write DNR orders to express their preferences in advance, at a time when they are capable of making informed decisions. These decisions are often made with regard to quality of life statements. The patient's perception of whether or not it is worthwhile to survive is based on his individual value judgements which may be influenced by religious views. Patients having lived nearly their full lifespan, living entirely dependent on others, or those with a severe underlying disease and a poor prognosis may choose to refuse life-prolonging treatment.[41] Others do not want to undergo the risk of a "nearly successful" resuscitation, with long-term intensive care treatment and without restoration of their previous health. Nevertheless, being chronically ill does not inevitably imply that the patient may refuse CPR.[41] It has been reported that even those elderly people who are severely ill or disabled opt for CPR.[17] An individual patient's expectation of CPR might not be *restitutio ad integrum*, but merely to extend his lifespan to allow participation in a forthcoming family event. Therefore physicians should assess carefully the factors which influence the patient's decision. The risk of provoking anxiety by discussing the appropriateness of resuscitation seems to be negligible.[37]

Physicians' attitudes

Respect for patient autonomy may be irrelevant when CPR has no potential benefit.[12] While patients may write a DNR order, physicians may also make a unilateral decision to withhold resuscitative attempts in a patient near death who is unable to communicate his preferences. In the patient suffering from a terminal disease, the physician's normal commitment to preserving life is not in accord with the patient's interests, if futile suffering is to be avoided. Restoring the circulation only prolongs the process of dying. If, because of the underlying disease, the patient is incapable of understanding the nature of a DNR decision and did not express preferences in advance, the options should, if appropriate, be discussed with the patient's relatives. Although the right of proxies to withhold or terminate life-sustaining treatment is not generally accepted, in the incompetent patient the physician often has to rely on the views of family members regarding the patient's potential wishes. In addition, family members may play an important role in the care of terminally ill patients, in particular if the patient is going to die at home. Relatives should be informed about the expected process of dying, possible events and their own reactions and behaviour. Patients and their relatives should be assured that any care necessary to relieve suffering will be given or continued, as withholding CPR does not mean withholding all medical treatment.[6]

In clinical practice the question arises to what extent patient preference is taken into account. Some resuscitation attempts may be performed on cardiac arrest patients who have a terminal disease and do not want the procedure. In a retrospective review, Dull and colleagues attempted to determine the percentage of resuscitation attempts which were unwanted or were undertaken in pre-hospital patients suffering conditions associated with poor survival rates.[22] Unwanted resuscitation was assumed if there was a living will, other advance directives or corresponding statements by family members or by the patient's private physician. One-third of all resuscitative attempts occurred in chronically ill patients (25%) or patients who did not want CPR (7%). The hospital discharge rate in both groups was lower than the discharge rate (16%) for cardiac arrest patients overall: 8% of patients suffering from chronic diseases and 2% who did not want to be resuscitated survived to hospital discharge.[22] These findings demonstrate the difficulties in elucidating pre-arrest conditions with poor prognoses and the limitations in honouring living wills and DNR orders in the field. Sometimes family members may panic in the face of death and call the emergency medical service, leading to unwanted resuscitation attempts.

On the other hand, the absence of a DNR order does not necessarily mean that any patient suffering from cardiac arrest receives full resuscitative efforts. The duration and intensity of advanced cardiac life support may vary depending on the physician's perception of the likelihood of benefit to the individual patient.[26] One factor associated with short resuscitative attempts in hospitalized patients was age more than 75 yr.[26] This finding and the results of a recently published survey of emergency physicians[38] support the hypothesis that age plays an important role in the decision to terminate unsuccessful CPR, although it is widely accepted that not age, but other factors such as co-morbidity and pre-arrest functional status are more important determinants of outcome.[30 48 49 51]

Clemency and Thompson surveyed anaesthetists to determine their opinions regarding DNR orders in the perioperative period.[18] Almost two-thirds of 190 responding anaesthetists assumed DNR-suspension and only 50% discussed this assumption with the patient.[18] If a patient with a DNR order suffers intraoperative arrest because of the underlying disease, 34% of anaesthetists interviewed said they would resuscitate; 68% would perform CPR if the patient had an iatrogenic-induced arrest during surgery.[16] The withholding and withdrawing of life support by critical care physicians had been analysed to determine current practice in adult intensive care medicine.[4] One-third of physicians were reported to have refused patients' or surrogates' wishes to discontinue treatment. Many physicians also reported the unilateral decision to withhold (83%) or withdraw (82%) life-sustaining treatment which they had judged to be futile, some of these decisions being made without the patient's knowledge and consent, and some despite their objections.[4] Often patients are not involved in discussions about their DNR status, or physicians write DNR orders at a time when the majority of patients are considered incompetent.[10] Even among seriously ill hospitalized patients, only a minority (29%) said they had discussed their CPR preferences with their physician.[41]

JUSTICE

This principle affects priorities in the allocation of health-care resources. Justice may be defined as giving to each person that which is due, and which can be claimed legitimately.[7]

CPR should be allocated throughout the community and within the hospital at a comparable level. It is a matter of justice to ensure some degree of equitable distribution of medical resources to all citizens.[2] Performing CPR which is inappropriate or futile may delay or prevent emergency treatment in other patients with a better chance of survival. This conflict is not restricted to CPR efforts or to the use of expensive and scarce resources, such as intensive care units and helicopters. In times when the demands on the health care system are competing heavily because of cutbacks in available public funds, it is increasingly important to provide fairness by common agreement.

Every citizen has the right to receive CPR. However, differences in survival of pre-hospital cardiac arrest patients related to race and socio-economic status have been identified.[9 29] In Chicago, Blacks were significantly less likely to undergo initially successful resuscitation, to be admitted to hospital or to survive until the time of discharge.[9] In Seattle, a higher socio-economic status was associated with a higher rate of survival.[29] Possible explanations include better access to health care and better state of general health. Witnessed cardiac arrests and bystander CPR were less frequent in Blacks,[9] whereas there were no differences in emergency service system response times and proportion of cases receiving advanced cardiac life support.[9 20] Interviews with emergency service system personnel in Oslo demonstrated that the social status of the patient did not influence the decision of whether or not to start CPR.[40]

Taking into account the serious shortage of organs suitable for transplantation, the use of expensive medical emergency resources in pre-hospital trauma management might be justified if it provided a source of organs. Young trauma victims with isolated, mortal head injury might be excellent candidates for organ donation if their vital functions can be maintained long enough to undergo organ evaluation.[19] The appropriateness of initiating or continuing life-sustaining therapies solely for the aim of organ procurement has to be questioned. The decision to resuscitate should be based primarily on each individual's chance to survive, taking the aspects of beneficence and nonmaleficence into consideration. Therefore, the aspect of organ procurement in resuscitation is an area of considerable sensitivity requiring further discussion.[2]

Conclusions

The question of the ranking between the different ethical principles is still a matter of discussion. Autonomy has been emphasized as the primary principle from which all others derive.[24] However, respect for autonomy is not the only principle and should not be overvalued if it conflicts with other aspects. In the clinical situation of cardiac arrest, the weight of respect for autonomy may be minimal while the weight of nonmaleficence and beneficence may be maximal.[7]

Physicians have an obligation to consider the therapeutic efficacy of CPR. The optimal solution would be to start resuscitation only in those patients with the potential for long-term survival (beneficence), but this can rarely be determined at an early stage.[14] In otherwise healthy individuals the standard of care remains prompt initiation of CPR. The time frame in cardiac arrest requires medical decision-making within seconds. Failure to administer prompt CPR would result in the patient's death.

Chronic or terminally ill patients should be encouraged to determine in advance whether resuscitative efforts should be initiated in the case of cardiac arrest. In these patients cardiac arrest is not a sudden event, but the end of the process of dying and therefore might be anticipated. Patients' preferences have to be assessed carefully in a compassionate way. Some patients may feel uncomfortable making life-or-death decisions, while others want to participate in the decision-making process. The in-hospital use of DNR orders seems to be increasingly common in several countries, whereas its acceptance in the pre-hospital setting is still a matter of debate.[1] Medical guidelines, ethical policies and legal conditions have to be developed to allow emergency service system personnel to respect the patient's autonomy in the field by honouring advance directives, without the fear of legal action. There is a clear need to discuss these issues in a public forum. We do not feel that it should be mandatory for every citizen to write advance directives, but public information and education should increase the number of people doing so voluntarily.

We feel that, in some instances, to save the patient's life might not be the *final* goal. Decisions taking into account the potential futility of treatment should consider the patient's perception of quality of life by respecting his individual hierarchy of values. To survive without restoration of pre-arrest health status may be of only limited benefit to the patient with serious advanced disease. Survival with physical or mental impairment may be strenuous. Sometimes resuscitative efforts save only to prolong the dying process, whereas sudden death from cardiac arrest could seem like a release.

If there is any doubt about the appropriateness of withholding resuscitative attempts, CPR should be initiated. Life-sustaining therapies can be withdrawn at a later time when proper medical, legal and ethical considerations have been addressed more thoroughly.[1] Training programmes have to be integrated into academic education to enable physicians to analyse and deal with ethical conflicts. The physician's moral decision should be based on the knowledge of the relevant ethical principles, remembering what is expressed in the Hippocratic oath: "I will use treatment to help the sick according to my ability and judgement (beneficence), but I will never use it to injure or wrong them (nonmalevolence)".[7]

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CORRESPONDENCE

Oxygenation criteria—a plea for more information

Sir,—We were interested to read the editorial by Peek and Firmin[1] arguing for the greater use of extracorporeal membrane oxygenation (ECMO) in the management of severe acute lung injury. Their results in Leicester seem impressive (although apparently unpublished elsewhere) and the authors issue a challenge to other units to match their 34% hospital survival rate in a similar group of patients. Unfortunately, however, they do not give enough information to allow this.

Values are given for the mean Murray score[2] and Pa_{O_2}/FI_{O_2} ratio in their group of 50, but more is needed if this category of patients is to be defined accurately and reproducibly. While a mean Pa_{O_2}/FI_{O_2} ratio of 8.7 provides an approximate indication of the problems with oxygen transfer in these patients, the picture is incomplete First, it would be helpful to know how long the problems persisted at this level before extracorporeal support was started; was it one or more hours or was the mean calculated from the single worst value for each patient and so based in each case on a single blood-gas result? Second, apart from the Murray score which includes positive end-expiratory pressure (PEEP) as one component, we are given little clue as to mean airway pressure at this time, despite the fact that this is accepted as being a major determinant of arterial oxygenation.[3]

As long ago as the 1970s the importance of at least some reference to airway pressure was recognized and the American ECMO study entry criteria reflected this by referring to specific levels of PEEP together with defined requirements for FI_{O_2} and Pa_{O_2}.[4] At the time, this was reasonable in that PEEP was the only commonly used means of increasing mean airway pressure. It is, of course, still used extensively and is one of the components of the Murray score. However, today, particularly in the most severe forms of acute lung injury, the extensive use of inverse ratio ventilation to maximize mean airway pressure means that its relationship to the level of PEEP is less predictable. It would be helpful, therefore, if future descriptions of severity of lung injury in patients undergoing ventilation could include data on the mean airway pressure being used.

M. S. NIELSEN
A. S. GRICE
Intensive Care Unit
Southampton General Hospital
Southampton

1. Peek GJ, Firmin RK. Extracorporeal membrane oxygenation, a favourable outcome? *British Journal of Anaesthesia* 1997; 78: 235–237.
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Sir,—We thank Drs Nielsen and Grice for their interest in our editorial. We agree fully with their comments that the Murray score and Pa_{O_2}/FI_{O_2} ratios do not provide a full picture of the severity and duration of respiratory failure. Unfortunately, it is not possible to discuss these factors in full within the framework of an editorial. Since the publication of our editorial we have heard that the detailed report of the patients alluded to has been accepted for publication in *Chest*. Data on duration of ventilation, airway pressures, minute ventilation and many other variables will be presented therein. We invite further discussion after publication of this paper.

G. J. PEEK
R. K. FIRMIN
Heartlink ECMO Centre
Glenfield Hospital
Leicester

Lateral positioning for regional analgesia during labour

Sir,—The letter by Richardson and Wissler[1] described several cases of labouring women who had extradural test doses while in the sitting position. They were placed in the left lateral recumbent position only after development of high spinal block. The sitting position may cause problems both in the spread of drug in the subarachnoid space, as highlighted by the authors, and also in the cardiovascular consequences of regional block.

Richardson, Lee and Wissler's initial report[2] suggested that cephalad spread in these cases may have been more extensive than would have been expected if patients were in the lateral position. Hamilton and Cohen also discussed extensive cephalad spread of isobaric solution while sitting as a factor in cases of high sensory block[3] or respiratory depression[4] after intrathecal sufentanil analgesia. Various "isobaric" solutions are hypobaric both *in vitro*[5] and *in vivo*.[6]

Richardson and Wissler changed their local anaesthetic test dose from lignocaine 45 mg to bupivacaine 5 mg Bupivacaine is theoretically safer if a high block results because of its greater sensory–motor differential than lignocaine. However, the dose of bupivacaine (0.25% solution 2 ml) may not be adequate. Stacey and colleagues[7] used bupivacaine 5 mg to produce spinal analgesia in labour. Although sympathetic block was usually present 5 min after this dose, analgesia was present in only two-thirds of patients and moderate to severe motor block did not develop in one-third of women. Furthermore, the deadspace of the extradural catheter and filter, if used, may vary from 0.25 to 1 ml. Therefore, only 2.5–4.375 mg of bupivacaine may enter the spinal canal. A large number of false negative test doses are to be expected.

The answer would seem to be to use a larger dose of bupivacaine, but manage the woman in the lateral position so that the effects of baricity alter lateral rather than cephalad spread.[6]

Position also has major effects on venous return. Sitting is associated with orthostatic stress on the circulation which may be combined with inferior vena caval compression during late pregnancy.[8 9] Greene and Brull[10] stressed the importance of a slight head-down tilt during spinal anaesthesia for this reason. Maintaining labouring women sitting after administration of isobaric spinal solutions or extradural test doses may result in greater hypotension than if they were lateral; this is exacerbated if the block is subsequently unexpectedly high.

The position in which the woman is managed for the first dose and thereafter usually follows on from the position chosen for insertion of the regional block. Vincent and Chestnut[9] found no overall difference in comfort if women curled up sitting and then lateral as for regional block, but in those who expressed a preference slimmer women preferred the lateral position and larger women preferred sitting. I ask women who request regional analgesia during labour which position they think will be most comfortable for insertion of the block, the majority indicate the lateral recumbent position rather than sitting. This is to be expected in our population with a low mean body mass index.[9] As far as the operator is concerned, anaesthetists who prefer to perform extradurals with the woman sitting find it harder if she is positioned laterally. The converse is not the case: if they prefer the lateral position for insertion, it is equally easy to place extradural catheters with the woman in either position.[11] Trainees should be encouraged to use the lateral position for regional block during labour, because there are occasions when this may be indicated clinically.[12]

I believe the lateral position to be optimal for administration of spinal or potentially spinal drugs, not only for the woman's comfort, but also in terms of safety. If the sitting position is deemed necessary for insertion of the block, consideration should be given to repositioning the woman into the lateral position, immediately (for intended spinal anaesthesia using isobaric solutions) or before an extradural test dose.

S. M. Kinsella
Directorate of Anaethesia
St Michael's Hospital
Bristol

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Sir,—We appreciate Dr Kinsella's interest in our letter. He and other authors continue to refer to non-glucose-containing anaesthetics as "isobaric solutions". We have shown that glucose-free local anaesthetics, opioids and combinations, commonly used for intrathecal administration for analgesia in labour, are hypobaric relative to the cerebrospinal fluid.[1,2] We and others have observed positional effects on the extent of block in labouring parturients which are likely to be attributable to the hypobaricity of the intrathecal injectate.[3] Although the clinical significance of hypobaricity and patient positioning as factors contributing to the extent of block remains to be fully elucidated, these solutions should no longer be referred to as isobaric.[1]

In 1981, Moore and Batra described the simultaneous injection of lignocaine and adrenaline as a test to detect occult i.v. or intrathecal placement of the extradural catheter.[4] Although they reported only on the predictive value of the i.v. component (adrenaline) in non-pregnant patients, their test dose rapidly gained acceptance for use in parturients. For years, investigators have focused on the safety, sensitivity and specificity of the i.v. component (adrenaline). Although the intrathecal component has received attention recently, we are unaware of any study that has evaluated the safety or predictive value of the intrathecal component of an extradural test dose in labouring parturients. Despite this, there is much published opinion on the correct test for intrathecal catheter detection in this population. The cases reported by us and others[5–7] serve to suggest that the local anaesthetic component (lignocaine 45 mg) described by Moore and Batra (and still used by many today) is excessive in the labouring parturient. This is not surprising, as relatively minuscule doses of intrathecal bupivacaine (with or without opioid) produce rapid and profound analgesia in labour. The current use of dilute anaesthetic solutions for extradural analgesia in labour has effectively eliminated the risk of systemic toxicity from the initial therapeutic dose, and has rightly focused our attention on the possibility of accidental high spinal block in the parturient.

Dr Kinsella suggests that the sensitivity of a 2-ml test dose containing bupivacaine 5 mg and adrenaline 15 μg in labouring parturients may be unacceptably low. Stacey and colleagues[8] administered the same dose of hypobaric bupivacaine (5 mg in 2 ml) to labouring parturients in the left lateral position (parturients were not moved after intrathecal injection). The authors reported detectable sensory analgesic levels and "substantial pain relief" in all 30 parturients. The extent of analgesic block varied considerably, probably attributable to inadequate cephalad spread of the hypobaric solution administered in the lateral position.[3] Subsequent to publication of our letter, we have detected two intrathecal catheters using the bupivacaine–adrenaline test dose. In both cases, sensory analgesia was detected promptly and seated parturients were moved to the lateral position; neither experienced significant changes in haemodynamic state and both had immediate and complete analgesia. Sensory blocks were dense and easily demonstrated and motor block was restricted to the lower extremities. The dramatic and rapid sensory and analgesic effects observed in both cases indicate to us that false negative intrathecal tests are very unlikely; we have not observed any thus far. However, in the event of a false negative test, the ensuing fractionated administration of the therapeutic dose (typically including fentanyl and a total of bupivacaine 12.5–20 mg) with the parturient positioned laterally further safeguards against the potentially catastrophic complications of high spinal block. We shall continue to use this testing method until further data become available.

Some investigators recommend extradural test doses containing amounts of bupivacaine known to rapidly produce high levels of dense sensory and motor anaesthesia adequate for Caesarean section.[9] We have never advocated such practice as there have been no studies on the safety of intrathecal injection of these large bupivacaine doses in labouring parturients who receive smaller amounts of i.v. prehydration. Although large intrathecal doses of bupivacaine produce dramatic effects, we believe that careful questioning and examination by the experienced anaesthetist at the time of administration of the test dose are preferable to induction of extensive and profound subarachnoid block in the labour room.

The clinical significance of positional effects on the haemodynamic state of the parturient has not been determined, and may or may not be influenced by feto–maternal health Today, it is not uncommon for healthy parturients to assume the upright position after administration of intrathecal and extradural local anaesthetics. We do not routinely dictate patient position during extradural catheter placement, but rather allow the parturient to chose the position most comfortable to her. We agree with Dr Kinsella's comments on development of skill in performing regional anaesthesia in parturients positioned laterally. Such practice undoubtedly contributes to success in performing spinal anaesthesia for many emergency Caesarean sections which would otherwise be performed under general anaesthesia.

M. G. Richardson
R. N. Wissler
Departments of Anesthesiology and Obstetrics and Gynecology
University of Rochester School of Medicine and Dentistry
Rochester, NY, USA

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Interactions between mivacurium and prilocaine

Sir,—In their study of mivacurium supplementation of i.v. regional anaesthesia with prilocaine in volunteers, Torrance, Lewer and Galletly noted that the duration of action of mivacurium was prolonged significantly beyond that which was expected, and that the incidence of systemic effects from prilocaine after tourniquet release was much increased when mivacurium was also given.[1] The authors did not provide any explanation for these phenomena and I would offer the following.

In common with all amide local anaesthetics (hence dibucaine number) prilocaine is a potent inhibitor of plasma cholinesterase.[2] Thus metabolism of mivacurium by plasma cholinesterase would be inhibited and its effects exaggerated. Until now, I have always thought of this as a theoretical, rather than a clinically relevant, interaction, but it is clearly important for mivacurium.

I wonder if the increased incidence of systemic effects of prilocaine after tourniquet release can be explained by some of the observations made during the study. Urticarial wheals were noted in two of the five volunteers who received mivacurium and prilocaine, and the authors concluded that the former produced an increase in vascular permeability. I would suggest that this might allow prilocaine to diffuse more rapidly into the blood from the tissues of the forearm after tourniquet release and so produce a more rapid increase in plasma concentration to a higher peak. Evidence of systemic effects would thus be more likely.

J. A. W. Wildsmith
University Department of Anaesthesia
Ninewells Hospital and Medical School
Dundee

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2. Zsigmond EK, Kothary SP, Flynn KB. In vitro inhibitory effect of amide-type local analgesics on normal and atypical human plasma cholinesterases. *Regional Anesthesia* 1978; 3/4: 7–9.

Sir,—We thank Dr Wildsmith for his comments. While inhibition of pseudocholinesterase by prilocaine in the isolated limb would explain the absence of mivacurium catabolism when the cuff was inflated, I would have expected two things to occur on cuff deflation: first, an influx of uninhibited pseudocholinesterase leading to mivacurium catabolism rather than prolonged weakness; and second, the small dose of mivacurium that was administered would redistribute throughout the body and become so diluted that its effect would be minimal. In this case the weakness remained localized to the arm and did not become generalized. I suggest therefore that the prolonged block produced by mivacurium in the isolated limb must be caused, at least in part, by the kinetics of mivacurium binding within the biophase of the limb.

The effect of altered vascular permeability on absorption of prilocaine might be investigated by measuring blood concentrations of prilocaine after prilocaine infiltration within the isolated limb, with and without a dose of i.v. mivacurium. We intend to investigate these interactions further.

J. McK Torrance
B. M. F. Lewer
D. C. Galletly
Department of Anaesthesia
Wellington Hospital
Wellington, NZ

Effects of volume on spinal anaesthesia with 0.25% hyperbaric bupivacaine

Sir,—Chung and colleagues[1] reported their clinical results on spinal anaesthesia with hyperbaric bupivacaine. Three groups (1, 2 and 3) of term parturients received 0.25% bupivacaine 3.2–3.6 ml (8–9 mg), 3.6–4.0 ml (9–10 mg) and 4.0–4.4 ml (10–11 mg) in 5% glucose, respectively. They found that cephalad spread of sensory analgesia was increased significantly with an increase in volume, and the onset time of sensory analgesia to T6 was significantly faster in group 3 than in group 1. The mean maximal level of analgesia in group 3 (T2–3) was significantly higher than that in groups 1 and 2 (T4–5 in each). They concluded that a large volume in itself may influence the spread of local anaesthetic in cerebrospinal fluid (CSF) and final block, especially in the narrow subarachnoid space of term parturients. Our clinical investigations with isobaric and hyperbaric amylocaine in parturients (King HK, Wood L, Khan AK. Spinal anaesthesia for Caesarean section. isobaric *vs* hyperbaric solution, unpublished data) and isobaric amylocaine in non-pregnant patients[2] produced similar results indicating that the volume of local anaesthetic is the most immediate significant factor affecting the extent of spread because of simple "bulk displacement" or area of contact; that is the greater the volume, the more extensive is the spread.

An anaesthetic solution administered into the subarachnoid space is diluted by CSF and absorbed by the neural tissues during spread. A hyperbaric solution has a density greater than that of CSF. When the patient is in the horizontal supine position, the subarachnoid space is inclined downward from the lumbar lordosis, towards the low-lying parts, in both caudad and cephalad directions, and the hyperbaric solution reaches the lowest points in both directions unless its baricity is decreased to CSF during the process. Additionally, we may surmise that when the drug concentration has reached its minimal pharmacologically active concentration, no clinical analgesia can be detected even if the solution spreads further. Moreover, sacral pooling of hyperbaric solution reduces the mass (effective dose, amount undetectable) of local anaesthetic that spreads cephalad and subsequently affects the results observed.

Chung and colleagues[1] used the same 0.25% hyperbaric bupivacaine solution. As increasing the volume of local anaesthetic solution implies an increase in drug dose, the results obtained may also have been affected by the dose of drug.[3 4] With multiple factors such as drug volume, dose and baricity/position effects, the claim that the results obtained in this study were caused by drug volume alone is not justifiable.

H.-K. King
Department of Anesthesiology
King/Drew Medical Center
Charles R. Drew University of Medicine and Science
Los Angeles, CA, USA

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3. King HK, Huntington C, Khan AK. Dose is the product of volume and concentration. *Regional Anesthesia* 1994; **19**: 431–432.
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Converting pH and H^+

Sir,—Further to the letter by Burden and McQuillan[1] on converting pH and H^+, I was taught the following trick nearly 30 yr ago by Professor Roy Simpson. Between pH 8.0 at 10 nmol $litre^{-1}$ hydrogen ion concentration and pH 7.0 at 100 nmol $litre^{-1}$, simply double or halve the hydrogen ion concentration for each 0.3 pH unit (table 1).

Table 1 Method of converting pH to H^+

pH	8.0	7.9	7.7	7.6	7.4	7.3	7.1	7.0
H^+	10	12·5	20	25	40	50	80	100

This method is easy to remember and a good demonstration of a logarithmic progression for juniors to learn.

P. T. Walling
Baylor Department of Anesthesiology and Pain Management
Baylor University Medical Center
Dallas, TX, USA

1. Burden RJ, McQuillan PJ. Converting pH and H$^+$: a "rule of thumb". *British Journal of Anaesthesia* 1997; 78. 479.

"Renal" dopamine

Sir,—We read with interest the recent study[1] and editorial[2] regarding the use of low-dose, "renal" dopamine. The study by Girbes and colleagues appeared to provide further evidence that the effects in question result from an increase in cardiac output. The editorial by McCrory and Cunningham concluded that attention to dobutamine should be considered. There are two important points which we feel have been overlooked.

First, in a study by Zaritsky and colleagues[3] on dopamine pharmacokinetics in critically ill infants and children, the authors concluded "substantial interindividual variation was observed in steady state dopamine clearance, . . . plasma dopamine could not be predicted accurately from the infusion rate". Different texts quote varying dose ranges for the renal–inotropic–vasoconstrictor effects of dopamine and this arouses suspicion. This study showed that with such pharmacodynamic variation it is impossible to predict the effects produced by a fixed rate infusion of dopamine in a critically ill patient.

Second, a study by Duke, Briedis and Weaver[4] compared low-dose dopamine with low-dose dobutamine. They studied 18 intensive care patients, each receiving, in random order, dopamine, dobutamine and placebo. They found a higher incidence of side effects with dopamine (tachycardia, hypertension, hypovolaemia and worsened Po_2/Fi_{O_2} ratio). The study found that while dopamine produced significant diuresis with no change in creatinine clearance, dobutamine produced significant improvement in creatinine clearance without diuresis.

Taken together these studies undermine the cosy rationale of "renal" dopamine. The pharmacodynamic case to justify infusion rate *vs* effects in intensive care is untenable. Dopamine appears to act as a diuretic but with side effects including those related to catecholamines. Dobutamine may not produce the gratifying increase in urine output but appears to produce improvement in renal function with less side effects. An increasing number of intensive care units are abandoning the uncritical use of dopamine and adopting a more scientific rationale for haemodynamic management. The recent study and editorial add to this evidence.

A. Inglis
Intensive Therapy Unit
G. Hilditch
Department of Anaesthesia
Western Infirmary
Glasgow

1. Girbes ARJ, Lieverse AG, Smit AJ, van Veldhuisen DJ, Zwaveling JH, Meijer S, Reitsma WD. Lack of specific renal haemodynamic effects of different doses of dopamine after infrarenal aortic surgery. *British Journal of Anaesthesia* 1996; 77: 753–757.
2. McCrory C, Cunningham AJ Low-dose dopamine: will there ever be a scientific rationale? *British Journal of Anaesthesia* 1997; 78: 350–351.
3. Zaritsky A, Lotze A, Stull R, Goldstein DS. Steady-state dopamine clearance in critically ill infants and children. *Critical Care Medicine* 1988; 16: 217–220.
4. Duke GJ, Briedis JH, Weaver RA. Renal support in critically ill patients: Low-dose dopamine or low-dose dobutamine? *Critical Care Medicine* 1994, 22: 1919–1925.

Sir,—Inglis and Hilditch refer to two important topics. First, they state that it is impossible to predict the effect of a given dose of dopamine because of the pharmacodynamic variation of dopamine. In our recently published study,[1] we also measured plasma dopamine concentrations by HPLC, as described in the article (table 1). In another yet unpublished study in seven healthy volunteers, dopamine at a rate of 4 $\mu g\ kg^{-1}\ min^{-1}$ was given during simultaneous infusion with different doses of noradrenaline while measuring systemic and renal haemodynamics. It is clear from the data that interindividual differences are substantial, which underscores the pharmacodynamic variation.

Table 1 Plasma concentrations of dopamine in patients (n=7) after infrarenal aortic surgery and in healthy volunteers (n=7) during simultaneous infusion with different doses of noradrenaline. Each time indicates 1 h of infusion. Plasma dopamine concentrations are represented as medians (interquartile range). nd=not detectable

Time (h)	Dopamine dose ($\mu g\ kg^{-1}\ min^{-1}$)	Plasma dopamine (nmol litre^{-1})
Patients		
Baseline	0	5.0 (2.7–11.3)
t1	2	297 (75–337)
t2	4	410 (110–683)
t3	8	413 (268–589)
t4	0	11·9 (9–108)
Healthy volunteers		
Baseline	0	nd
t1	4	463 (263–669)
t2	4	710 (327–1104)
t3	4	664 (345–934)
t4	0	nd

However, another important feature of dopamine should be mentioned, that is the different sensitivity and effects in different patient groups (and individuals). Our group and others have reported on these different effects of dopamine (agonists) with respect to renal haemodynamic state and plasma noradrenaline concentrations. In patients with a glomerular filtration rate (GFR) <50 ml 1.73 m^{-2}, dopamine was unable to increase GFR or renal blood flow.[2] The effect on renal haemodynamics in patients with congestive heart failure is, in contrast, more pronounced than in healthy volunteers.[3] The same is true for the DA_2 receptor stimulation related suppression of noradrenaline release from the presynaptic terminal of sympathetic nerves.[4] Furthermore, it has been shown, or at least been shown highly likely, that the response to DA_1 receptor stimulation is genetically determined.[5 6]

With respect to the second remark by Inglis and Hilditch, we agree that it becomes more and more clear that the renal haemodynamic effects result mainly from the systemic haemodynamic effects of dopamine. We disagree however with their conclusion that dobutamine produces less side effects, based on a single study. Furthermore, the cited study by Duke, Briedis and Weaver[7] mentioned tachycardia and hypertension in four and three of 18 patients as a side effect of dobutamine, respectively. An important flaw of this study, in our view, is the introduction of carry-over effects of dobutamine because of the sequential design. We agree however, that the uncritical use of dopamine (as a "renal" dose) should be abandoned, but the same holds true for dobutamine Low-dose dopamine is probably a useful drug in the initial treatment of (severe) congestive heart failure and will remain useful in the initial treatment of hypotensive patients, in whom the diagnosis is not yet established.[8]

A. R. J. Girbes
K. Hoogenberg
A. J. Smit
Surgical Intensive Care
University Hospital Groningen
Groningen, The Netherlands

1. Girbes ARJ, Lieverse AG, Smit AJ, van Veldhuisen DJ, Zwaveling JH, Meijer S, Reitsma WD. Lack of specific renal haemodynamic effects of different doses of dopamine after infrarenal aortic surgery. *British Journal of Anaesthesia* 1996; 77: 753–757.
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Einfluss von Dopamine auf Haemodynamik und Nierenfunktion bei der schweren Herzinsuffizienz des Menschen. *Klinische Wochenschrift* 1973; **51**: 549–556.

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British Journal of Anaesthesia 1997; **79**: 265–267

BOOK REVIEWS

Manual of Drug Interactions for Anesthesiology, 3rd Edn. R. A. MUELLER AND D. B. A. LUNDBERG Published by Churchill Livingstone, Edinburgh. Pp. 503; indexed; illustrated Price £30.00.

This is a manual aimed at the practising anaesthetist which, despite its title, is more concerned with side effects than true drug interactions. The authors have concentrated on reactions between anaesthetic drugs and concomitant medication rather than those between non-anaesthetic drugs.

The book is in three sections: an index, a general chapter entitled the "Philosophy and theory" of drug interactions, and a catalogue of side effects and drug interactions. The index is comprehensive and an effort has been made to include British and North American drug names. This is not always consistent, for example lignocaine but not pethidine, adrenaline but not noradrenaline. Anaesthetic drugs are not included in the index but are referred to under the drug with which they are said to interact. The general chapter comprises approximately 5% of the book and documents the pharmacokinetic and pharmacodynamic factors which may be responsible for drug interactions. Although this is probably the best part of the book, and the only part which is referenced, it offers no particular insights beyond those obtainable in any number of pharmacological textbooks. Finally, groups of drugs are catalogued according to their principal clinical usage—antihistamines, anti-infectives, antimitotics through to hormone agonists/antagonists and miscellaneous.

One of the difficulties of a manual such as this is defining what is meant by a drug interaction. The authors have not highlighted those interactions which might be considered dangerous, and equal weight is given to reactions which most clinicians would regard as trivial, for example halogenated hydrocarbons and vitamin E, glipizide, tolbutamide, imipramine and phenytoin. Unfortunately, some of the information is incorrect or misleading. There is no evidence that, in normal doses, diazepam reduces arterial pressure except in the presence of hypovolaemia. Meperidine (pethidine) (p. 333) does not increase smooth muscle tone and induce spasm of the sphincter of Oddi—quite the opposite!

Some of the statements veer on the egregious. For example, under the heading of "lidocaine" (p. 250) the authors state that, "as in all patients requiring antiarrhythmic therapy, the use of volatile halogenated hydrocarbon anaesthetics is probably contraindicated". Does this include the ethers or just halothane, and where is the evidence for such a claim? Similarly, they advise against nitrous oxide for "long cases" in patients receiving paracetamol unless the granulocyte count is normal. They also warn of hypothermia in these patients! Has the surgeon nothing to do with this? Under indomethacin (p. 317) the authors advise against general anaesthesia with halogenated hydrocarbon anaesthetics and nitrous oxide.

Surprisingly, there is no mention of interactions between sevoflurane (and other ethers) and soda-lime or Baralyme. The very dangerous interaction (torsades de pointes) between cisapride and fluconazole (or other antifungal drugs) is also ignored despite the potential for co-administration in the intensive care unit.

There is little useful information on drug interactions in this manual that cannot be found in a more authoritative form in appendix 1 of the much-maligned, freely distributed *British National Formulary*.

J. P. H. Fee

Critical Care, 3rd Edn. J M. CIVETTA, R. W. TAYLOR AND R. R. KIRBY (editors). Published by Lippincott-Raven, Philadelphia. Pp. 2363; indexed; illustrated.

This is a tome: a 2300-page, 3-inch thick, 9lb 4oz book, with 206 contributors who have marshalled their thoughts into 156 chapters. With a book such as this, there was little chance to do justice to it by reading it from cover to cover, so I asked myself the purpose of such a book, in the age of the CD and the laptop computer. Quite simply, despite all our electronic aids, we shall not be able to do without mammoth textbooks for years to come. It is the means by which we obtain information at 03:00 (or when the SHO rings you at home). We require a large reasonably up-to-date text in which we can find information easily and (when the need arises) obtain in-depth information in one source. This "source" has made it to the third edition. Our laptops still have someway to go in replacing paper, despite their modems and search facilities.

I started with the index: it is comprehensive, covering 80 pages of three columns of 10-pt print (equivalent to approximately 5% of the book). I looked up treatment on my most recent ICU admission: lithium poisoning. Although there was much on toxicology and clinical manifestations there was little detail on treatment: the ICU physician will usually be presented with the diagnosis. My initial (non-statistically valid) enthusiasm for the text was under threat.

I looked over the chapter headings. The book is divided into 17 sections, each with a variable number of chapters. Sections cover the usually expected areas, for example pathophysiology, monitoring, organ failure, etc, but also the unusual decision making, rheumatic disorders. Although I did not read the preface first (!) I noted that there was a clear editorial decision to have a standard opening "Immediate concerns", with a subheading "Stress points", suggesting that anything of importance (I would have presumed "clinical importance") would be mentioned in this opening. This is not quite what happens in every chapter, and discloses the American origin of the text. Thus for the chapter entitled "Vascular cannulation", an early "immediate concern" is the discussion between the operator and patient on the benefits, risks and alternatives of the chosen techniques (the medico-legal aspects?). I cannot see this happening in the UK when presented with patients on whom we most commonly use our skills (i.e emergencies) who are often unable to communicate. In the same chapter, there is discussion about the Allen (sic) test. The authors state that they do not advocate its use: when will we simply admit that it is not done and is of no benefit! Other chapters (and "immediate concerns") are good and precise, for example "phaeochromocytoma", which has a chapter of its own, and which I read in detail to see if I was doing it correctly! However, interesting though it was, does phaeochromocytoma deserve eight pages when ARDS is covered in only 16 pages? I was also particularly interested by the good chapter on respiratory muscle fatigue, but it got lost in the chapter on mechanical ventilation There is further evidence of the North American–European divide: American "BIPAP" (bilevel positive airway pressure") for non-intubated ventilatory support and (unmentioned) European "BiPAP" (biphasic positive airway pressure) for patients receiving preset pressure controlled ventilation.

Throughout my time with this book, I have looked up individual topics and generally grazed with little malice aforethought. The book is clearly American, and reflects American practice It spans much greater areas and includes topics in the UK that would not usually be included in a critical care text (e.g. hypertensive urgencies) and drugs not usually used or unavailable (e.g. nicardipine for hypertension, acetylcysteine to liquefy sputum). In the end, what I liked best about the book was the opening section on "decision making" which included such topics as "how to read a paper" in addition to ethical decision making.

What did I think of the book overall? I liked it much better than in the words of Alan Wicker "some others I could name". It is a well illustrated, well researched, comprehensive necessary evil This book, or something similar, is a required bench book in every ICU. Placing it in the hospital library is a waste of a resource. Most chapters have up-to-date (1995) references, although in one (chapter 145) the most up-to-date reference was 1985. However, this is not the curate's egg. Most of it is good.

P. G. Lawler

Pain Management for the Practising Physician. G A. IRVING AND M WALLANCE. Published by Churchill Livingstone, Edinburgh. Pp. 330; indexed, illustrated. Price £32.50.

The authors' have aimed this text at medical students, house officers and general practitioners to provide easy to follow advice on pain management for non-pain specialists. The book is divided into five sections and is preceded by an introduction which contains a useful glossary of pain terminology. Section 1 provides essentials of pain anatomy, physiology and pharmacology, although there are one or two errors, for example the sigma receptor is defined as an opioid receptor. Section 2, which comprises approximately two-thirds of the book, consists of short chapters on various pain conditions presented in alphabetical order. The emphasis is very much on treatment and this is presented in outline in the form of algorithms with supporting text. In addition, each chapter concludes with a case study, which emphasizes the multimodal approach to pain management which does not appear obvious in the algorithms. Section 3 presents a useful introduction into psychological aspects of pain management, and sections 4 and 5 cover non-pharmacological pain therapies and possible future treatments, respectively.

This book provides an easily read introduction to pain management, although the general style makes it very repetitive. The authors' personal opinions are clearly prevalent, particularly with regard to treatment algorithms. The algorithms and guidelines give the impression that, armed with this book, junior doctors should be able to tackle most chronic pain patients, but it lacks advice on history and examination of the pain patient which is relevant for those to whom the book is aimed. On the other hand, general practitioners may find this book of more practical use.

R. Atcheson

The Pulmonary Circulation: Moving From Passive to Active Control. M. R PINSKY, J.-F. DHAINAUT AND A. ARTIGAS (editors). Published by WB Saunders, London. Pp. 295; indexed; illustrated. Price £45.00.

This book contains the proceedings of an international symposium on the pulmonary circulation which took place in 1995. It consists of 19 chapters written by international experts from both sides of the Atlantic. The quality and length of the chapters are extremely variable; there are excellent reviews of endothelin and other pulmonary vasoconstrictors, leucocyte migration and mechanisms of pulmonary oedema formation. There are also several reports of original research, including work on the cardiopulmonary effect of home oxygen therapy and the combined effect of inhaled nitric oxide and pulmonary vasoconstrictors.

There is inevitably a large amount of duplication within the book. The mechanisms of action of nitric oxide, and details of the endothelin and arachadonic acid pathways appear in multiple chapters.

At a price of £45 this book might be a useful purchase for the library or department with an interest in this field, but is not a book for the general anaesthetist or intensivist's personal collection.

J. D. Young

The Pulmonary Artery Catheter in Critical Care—A Concise Handbook. C. PERRET, D. TAGAN, F. FEIHL AND J. J. MARINE. Published by Blackwell Science, Oxford. Pp. 940; indexed; illustrated. Price £55 00.

This concise book is an excellent reference manual for the use of a pulmonary artery catheter. In the preface the authors highlight the criticism that pulmonary artery catheters are used frequently with woefully inadequate expertise and this text seeks to provide a "quick and easy" source of both practical and theoretical information. It succeeds. The book is well laid out with easy access to the wealth of information within it. It is comprehensive, covering insertion techniques through measurement problems to the meaning and use of derived values: it has a large selection of case studies. The diagrams are clear, relevant and numerous.

The authors have placed pertinent references at the bottom of the relevant page which makes it very effective in its use as a reference text. There are useful lists of symbols, abbreviations and formulae and there is a short but informative section on definitions which describes both the meaning and misconceptions of commonly used terms, such as preload and afterload.

If there is a significant criticism it is that the authors appear to have a strong bias towards the positive aspects of the use of the catheter and do not address the issue of its genuine clinical value. The extensive list of indications is not balanced by a larger list of situations where the cost benefit of placing the catheter mitigates against its use.

I think this is an excellent book to have in the ICU. This book should be recommended reading for those who confidently use pulmonary artery catheters and compulsory reading for those being trained in their use.

N. Soni

Hyperthermic and Hypermetabolic Disorders. P. M. HOPKINS AND F. R. ELLIS (editors). Published by Cambridge University Press, Cambridge. Pp 286; indexed. £50.00.

It has long been a contention by some North American workers in malignant hyperthermia (MH) that the condition can be triggered by factors other than exposure to the relevant anaesthetic agents, as in the pig; for example trauma, stress and severe exercise. No such condition has yet been described convincingly in Europe This text, edited by two of the leading authorities on MH in Europe, both from the Leeds MH investigation unit, appears to have been written with the underlying assumption that such a link may exist. The book is divided into two main sections: the first covers exertional heat stroke and the second malignant hyperthermia. There are seven chapters in each section, with a third section of three chapters (one on neuroleptic malignant syndrome, one on drug overdose (tricyclics antidepressants, amphetamines, cocaine, anticholinergics, etc.) and one on endocrine (thyroid and adrenal) disease). The main thrust is exertion-induced heat injury and MH.

The exertional hyperthermia section is practical, with the first two chapters based on experience in the armed forces, principally the army. (Naval and air force personnel apparently rarely suffer from the condition.) The emphasis is on precipitating factors and clinical management, leading to discussion of the physiological testing of subjects' susceptibility to heat, the use of nuclear magnetic resonance spectroscopy to investigate muscle metabolism and ending with a review of *in vitro* muscle contracture testing for MH in heat injury victims; all of this is inconclusive other than that some individuals who become hyperthermic with exercise have a myopathy which responds in an equivocal manner to the various MH *in vitro* contracture tests.

The second seven chapters comprise an up-to-date and detailed review of MH, including details, with tracings, of the various *in vitro* tests carried out in confirming, or excluding, the diagnosis. This part should be prescribed reading for all examination candidates and for those referring patients for investigation.

I found much of the first part of this book too anecdotal, although with such a condition this is probably inevitable. I felt also that it could have benefited from an introductory chapter on thermal physiology in general to bring together all the various mechanisms and conditions discussed, and in this respect the book felt somewhat disjointed. It is however very readable and informative and I would strongly recommend it, particularly for its detailed account of the diagnostic laboratory investigations, to all those responsible for running their departmental libraries.

I. T. Campbell

Intensive Care Manual, 4th Edn. T. E. OH (editor). Published by Butterworth–Heinemann, Oxford. Pp. 1032; indexed; illustrated. Price £40.00.

The fourth edition of the successful *Intensive Care Manual* continues to bridge the gap between the weighty, comprehensive reference text and the smaller, more abridged handbook. First published in 1979, the *Intensive Care Manual* has developed into a substantial volume that could be described as either a concise textbook or a comprehensive manual. The fourth edition comprises 18 sections covering a spectrum of broad headings, for example organization aspects, acute coronary care, respiratory failure, neurological disorders, etc. Each section is made up of 4–10 chapters representing a total of 110 chapters in 1032 pages. Each chapter contains numerous references, which are either contemporary or landmark papers, and provide the reader with the option to research a subject in more detail. To produce such a huge amount of easily accessible and readable factual information the editor has drawn upon a team of 63 contributors, most of whom are dedicated intensivists. Despite this the style and format are remarkably uniform with little of the redundant, superfluous prose found in many textbooks.

It is not possible to describe all the additional material that has been incorporated into this edition but most of it represents either recent advances or topical issues in the specialty. There is a new chapter on severe soft tissue infections which contains a concise, well-referenced section on necrotizing fasciitis and a chapter on meningitis and encephalomyelitis that excludes, surprisingly, a description of herpes simplex infection. There is a larger, more inclusive, section on paediatric intensive care and coverage of haematological malignancies and immune deficiency syndrome is expanded.

Overall the *Intensive Care Manual* covers a wide range of relevant and accessible information, presented in a concise and lucid manner. It provides comprehensive practical guidance for both routine and complex diagnostic and therapeutic decisions. I would recommend this book as the primary text for every trainee in the field of intensive care and that a copy be held in every intensive care unit for the immediate use of consultants, trainees and nurses.

D. Turner

Critical Care Medicine: Perioperative Management. M. MURRAY, D. COURSIN, R. PEARL AND D. PROUGH (editors). Published by Lippincott–Raven, Philadelphia. Pp. 315; indexed; illustrated.

This book envisages a role for anaesthesiologists in the United States of America similar to the role that anaesthetists in the UK already occupy. It is aimed at the anaesthesiologist with foresight, the specialist in perioperative care who is not only a clinician but also a politician, an educator and a businessman.

Perioperative care differs from critical care, which in the USA is fragmented and rarely involves anaesthesiologists. The editors see the important components of perioperative care as: expeditious preoperative assessment, careful anaesthetic management and appropriate postoperative care with particular expertise in airway and cannulation skills, and emergency medical care. The foreword indicates how this vision of the future applies to anaesthesiology. The anaesthesiologist will become a physician outside the operating room exercising his skills in crisis management and teamwork. The statement that the *new* anaesthesiologist will have a rewarding career sounds like a recruitment drive but suggests that the old anaesthesiologist does not.

There are some good areas covered in the book. In section 1, "organization of an intensive care unit, patient assessment and general critical care", the chapter on ethics stands out. It discusses with insight the changing ethical balance from doing the best one can for an individual patient and respecting their autonomy to exercising responsibility for the health of society as a whole with access to care for all and justice as a guiding principle. This is as relevant in the UK as it is in the USA. The discussion on the appropriate use of do not resuscitate orders during operation and the need to clarify and review such orders regularly should be read by all anaesthetists.

The second and third sections cover organ specific critical care and critical care in particular clinical circumstances. Generally these chapters are well written and provide comprehensive reviews of their subjects. The chapter on endocrine emergencies is an unusual addition which provides useful information in a clear manner.

Overall the chapters have a user friendly format. Each contains a summary, key points and an "eye to the future" section on future developments. These sections provide useful, quick reference summaries of the chapter; a volume of the "key points" would make a useful handbook.

Other parts of the book deserve mention out of interest. The chapter on quality management demonstrates the convergence of American and British health systems. Quality management is driven by insurance companies in the USA but change the name to purchasers and the same principles apply in the UK. The chapter on organization of an intensive care unit details the various members of the team and what they do, but there is no mention of trainees and the important role they play. This chapter would also benefit from a discussion of teamwork principles and of the training and educational role of intensive care. Section 1 ends with several chapters on perioperative interventions and pathophysiology. This is an odd group of chapters, ranging from intubation and cannulation skills to acid–base balance. The choice seems rather haphazard but presumably reflects American practice.

The strength of anaesthesia in the UK lies in our knowledge of normal physiology and pharmacology and our understanding of how that changes in a variety of clinical circumstances Although this book has basic science content, overall it fails to apply this clinically. There are better books on critical care and better anaesthetic books.

This book makes me proud to be an anaesthetist in the UK where anaesthesia is a recognized and respected specialty. Anaesthesiology in the USA has much to learn from the UK in terms of perioperative medicine. Interestingly, there are two Irish contributors but none from the UK. It is unfortunate that our American colleagues need this book.

M. P. Shelly

Stabilisation and Transport of the Critically Ill. N. S. MORTON, M. M. POLLACK AND P. G. M. WALLACE (editors). Published by Churchill Livingstone, Edinburgh. Pp. 256; indexed; illustrated. Price £42.50.

All anaesthetists will be familiar with the difficulties in providing safe transport for critically ill patients, both within hospital and between centres. This book brings together experts in this field and reviews scientific background and research evidence providing practical advice on the transport of these patients. It includes international experience and difficulties with particular patient groups, for example children, and closes with a section on audit, research and outcome.

It is essential reading, therefore, for those interested in, or planning, a transport service but its value to a more general readership is more questionable. There is considerable variability between chapters in both quality and content. For example, the chapter on paediatric transport is 72 pages in length and includes detailed information on paediatric intensive care that goes beyond the requirements of this book, while the chapter on head injury transport is only 17 pages in length and contains little that is not covered elsewhere in the text. As the latter is one of the commoner conditions requiring transfer, more detail would be appropriate. The final chapter on research and audit hardly mentions transport and is, in effect, a brief academic introduction to these topics.

There is considerable repetition, and many details of practical aspects, which many readers will be seeking, are difficult to find as they are included in more general chapters. The section on equipment is perhaps too specific as it recommends a particular make and model of monitor which will, almost certainly, be improved or replaced in the near future. The underlying principle of safe transport—that patients should be stabilized first and accompanied by suitably experienced and equipped staff—is emphasized repeatedly and I am sure that this is correct as failure to do this may result in tragedy. However, publicity on transfer of critically ill patients usually criticizes the fact that they require transfer rather than how it is done. A more positive approach and a higher profile for transport facilities may change this and this book is certainly a step in that direction. The production quality is generally good although some of the photographs are not particularly clear. If it is intended to function as a practical manual, it needs some reorganization; perhaps soft covers would make it more durable in addition to lowering the cost to a level that could make it an essential purchase for all intensive care units and other departments who find themselves involved with the transport of the seriously ill.

G. S. Routh

British Journal of Anaesthesia 1997; **79:** 268

ERRATA

British Journal of Anaesthesia 1997; 78: 601–605.

p. 603. There was an error in equation (3) in which superscripted numbers were printed in normal case. Therefore, equation (3) should read:

$S = 3.207W^{0.7285-0.0188\log W}H^{0.3}$

British Journal of Anaesthesia 1997; 78: 618–625.

p. 623. There was an error in figure 6. In part D of the figure, the rectangle labelled "VE–VD" extends to the height of the dotted line, instead of stopping level with the top of the rectangle in part C. The corrected version of figure 6 is printed below.

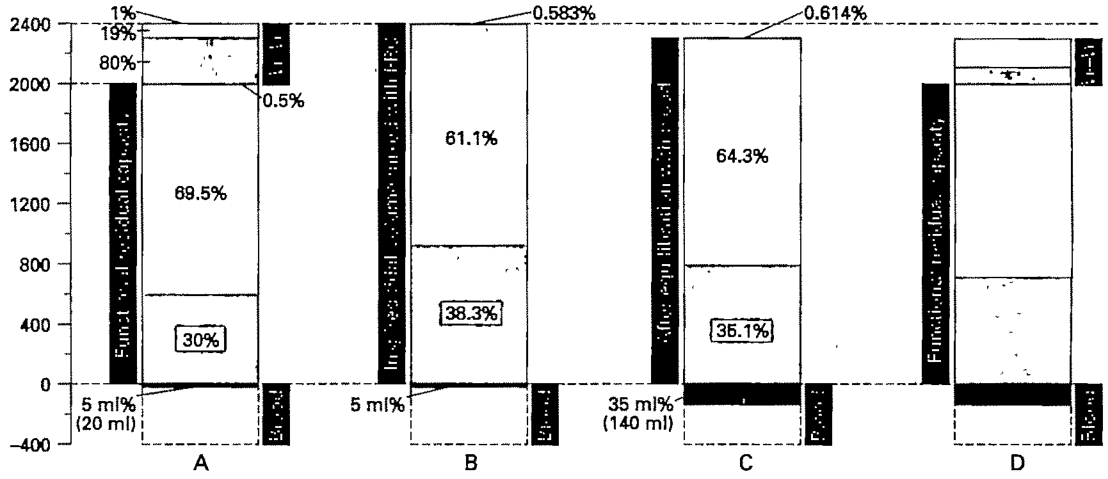

Figure 6 Constant inflow case with FRC and recirculation of anaesthetic. Single respiratory cycle during washin of nitrous oxide. An inspired mixture of 1% second gas (black), 19% oxygen (white) and 80% nitrous oxide (light shading) is used with a non-rebreathing system. The *Y*-axis shows the volume of gas or blood (ml). A: From top down, 400 ml of inspired gas mixture ($V_I - V_D$); FRC 2 litre comprising 0.5% of the second gas, 69.5% oxygen and 30% nitrous oxide; 400 ml of blood for equilibration containing 20 ml of recirculated nitrous oxide (black areas). B: After complete mixing of inspired gas with FRC. C: After equilibration of gas with 400 ml of blood ($\lambda = 1$ for nitrous oxide and 0 for oxygen and the second gas). Dissolved nitrous oxide is shown as black. D: From top down, expired alveolar tidal volume ($V_E - V_D$) = 280 ml, FRC (still 2 litre) and blood, after equilibration.

We apologize to the authors for these errors which arose during the editorial process.

"I would have everie man write what he knowes and no more."—MONTAIGNE

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EDITORIAL I

So just who was James "Young" Simpson?

November 4, 1997, sees the last of the major sesquicentenary anniversaries in our specialty—the discovery of the anaesthetic effects of chloroform. The event is being marked a little early with a meeting this month in Edinburgh, celebrating not so much the discovery of chloroform, but the whole contribution to medicine of the discoverer, James Young Simpson. Who was this man, who unlike many other early pioneers of anaesthesia was already a major medical figure at the time of his involvement? He was Professor of Midwifery at Edinburgh University, was well regarded as a lecturer, had an extensive clinical practice and had just been appointed physician to Queen Victoria. This was a member of the establishment yet he challenged the perspective of the medical world by enthusiastically embracing and advocating the use of anaesthesia, sometimes against considerable opposition.

James Simpson was born to poor parents, his father being a baker in Bathgate near Edinburgh.[1] Because he had shown aptitude at school his father and elder brothers scraped together enough money for him to attend Edinburgh University, which he entered at the age of 14 to study the arts. However, after 1 yr he transferred to the medical course and graduated 1 month before his 19th birthday, working initially as a doctor's assistant. During this time he prepared and submitted an MD thesis entitled *Death by Inflammation* which brought him to the attention of the Professor of Pathology in Edinburgh, John Thomson, who offered him employment and soon suggested obstetrics as a good career for an ambitious man. Simpson threw himself into its study and within 3 yr he was recognized as the producer of both quality research and inspiring lectures.

In November 1839, at the age of 28 yr, and at sometime having acquired the sobriquet "Young", he applied for the vacant Chair of Midwifery in Edinburgh, an appointment determined by the Lord Provost, magistrates and town council. Simpson spent £500, an extraordinary amount of money then (he was paid only £50 per annum 6 yr previously) on promoting himself and pressurizing the members of the council to vote for him. One of the criticisms raised against him was his bachelor status, a problem which he quickly overcame by proposing to a relative, Jessie Grindlay, whom he married in Liverpool on December 26, 1839. They promptly returned to Edinburgh where Simpson continued canvassing and the new Mrs Simpson was put to work cataloguing and preparing a portfolio of teaching material, possession of which was a prerequisite for the post. Their efforts were successful and the Chair was won on February 4, 1840, by one vote.[1]

During the next 7 yr he was formidably busy with both clinical and university activities. He was recognized as a leading obstetrician and the family home was always full of visiting doctors and private patients, some travelling from far afield. Despite, or perhaps because of, his enormous workload, Simpson was an obstetric innovator, devising an "air tractor" (a suction device to extract babies[2]), encouraging the use of the speculum in diagnosis and advocating hysterectomy for carcinoma. To the modern obstetrician such things are routine, but his specialty was then still in its infancy. Forceps had been available for more than 100 yr, but there was much prejudice against their use and cautery was the only treatment for uterine cancer.

Simpson also continued to be interested in general medicine and surgery, and was particularly concerned about the high rates of death after both operation and childbirth in hospital. His own statistics revealed that 1 in 53 women died postpartum in the Edinburgh Royal Maternity Hospital (the majority of puerperal fever), compared with 1 in 270 in the community.[3] This difference he attributed to cramped, dirty conditions, and he wrote of the detrimental effects of hospitalization and considered how hospitals might be better designed to minimize mortality. To confirm that hospital size and overcrowding influenced mortality, he conducted an extensive postal survey of death after traumatic and non-traumatic limb amputation in all major and cottage hospitals in the UK. Over a 10-yr period he confirmed that mortality in major hospitals was greater than in smaller units and proposed that hospitals be designed with this in mind. In addition, anything unusual attracted Simpson's attention. For example, he investigated the popular belief that a woman born with a male twin was infertile.[4] Apparently this is true of cows, something he confirmed by visiting slaughter houses and interviewing farmers, but data on childless marriages collected from two nearby towns, Bathgate and Grangemouth, showed that the fertility of women with male twins was no different to others.

In the midst of all this activity came his great claim to popular fame. Being innovative and receptive to new ideas he was immediately excited by the news from London of the successful use of ether to produce anaesthesia by Squire and Liston in December 1846. He travelled south before

Christmas to meet Liston and watch ether being used. Returning to Edinburgh he immediately used it in his own practice, initially as an anaesthetic for surgical interventions during delivery, but later for analgesia during normal labour. He publicized this use of ether, but was quickly criticized by the medical profession because of concerns about the morality and safety of providing analgesia/anaesthesia to labouring women. Simpson virtually waged war with the profession over the ethical issue, combining his own extensive knowledge of the bible with logical argument to refute the supposed religious reasons that prevented the use of anaesthesia in these patients and publishing his arguments in widely distributed pamphlets. To deal with the safety aspect Simpson used data from the Dublin Lying-in Hospital to show that mortality increased with duration of labour. He argued that anaesthesia and effective analgesia would decrease this mortality by allowing intervention and shortening labour. Of etherization he wrote: "I have no doubt whatever, that some years hence the practice will be general. Obstetricians may oppose it, but I believe our patients themselves will force the use of it upon the profession".

However, Simpson was quickly dissatisfied with ether, mainly because of its flammability and long induction time, and he sought alternatives by inhaling many chemicals with his assistants. In 1847, responding to a suggestion from David Waldie, a Liverpool chemist, chloroform was tried. Simpson, impressed with the results, reported his discovery and set about introducing chloroform into clinical practice, but he was still attacked for championing the use of anaesthesia. To challenge those who doubted its safety Simpson again turned to a large scale statistical survey, analysing both the rate and mode of death after limb amputation in patients treated with and without anaesthesia. Although the difference was small the mortality rate was slightly lower in the anaesthetized group and Simpson used these data to convince the last doubting surgeons that anaesthesia was safe.

Because of its ease of administration, chloroform soon became the most popular anaesthetic agent in the UK, but it was not long before deaths associated with its use were reported. Simpson claimed that improper administration, not a fundamental drug problem, was to blame and it was 1911 before the issue was finally resolved with the demonstration that chloroform can produce ventricular fibrillation.[5] Simpson is often criticized for his failure to concede that chloroform caused deaths and is portrayed as a man well satisfied, resting on his laurels. However, his own works reveal that this was not the case for he was always looking for better solutions. For example, he reasoned that even greater benefit would accrue if it were possible to provide anaesthesia of the surgical field alone and he was the first to use the term "local anaesthesia". He investigated the ability of compounds such as ether, benzene and chloroform to produce topical anaesthesia, and found that some "numbing" could occur with chloroform. This was inadequate for surgery, but he hoped that "some new facts and precepts may be elicited that will enable both the physician and surgeon to exhibit and apply local anaesthetics with more science, precision, and success than hitherto".

Despite all these activities Simpson's original interest in wound inflammation continued, with careful observation and research again supporting his proposals. Having seen many patients with bullet wounds, but no evidence of inflammation, he concluded that surgical wound inflammation was caused by the suture material and he proposed that metal thread should be used instead. To confirm this he carried out animal experiments[6] and later reported the successful use of platinum wire to achieve primary healing in patients. He also suggested that metal pins (removed a day later) should be applied through the skin to compress bleeding vessels.[7] This technique, called acupressure, resulted in less wound breakdown and late haemorrhage, but it required meticulous care and most surgeons quickly abandoned its use, although those who persevered achieved very good results.

As a result of his work, Simpson achieved many honours, including the Presidency of the Royal College of Physicians of Edinburgh and culminating in the award of a Baronetcy in 1866. He died in 1870 and a Westminister Abbey burial was offered to his family, but this was refused and he was buried in Warriston cemetery, Edinburgh, beside the children who had predeceased him. On the day of the burial a service was held at his home for family and friends, and many other services were held around the city. Afterwards the crowds converged on Simpson's home, where a funeral procession a mile long and involving 2000 people was organized. A crowd estimated at 80 000 watched it pass.[8] Despite this large show of public grief, Simpson was obviously not liked by all. No one achieves so much without ambition, and ambition can be a negative in addition to a positive force. His obituary in the *British Medical Journal* makes interesting reading and clearly was not written by a supporter. It states that his greatest work was the attempt to diminish the mortality of surgical hospitals, although it concedes that "he may claim the chief share of whatever credit belongs to the recommendation of the general employment of anaesthesia in midwifery practice" and "the position of JYS in reference to anaesthetics may be easily stated. He had, of course, no claim whatever to their introduction, nor is it probable that their general acceptance would have waited for his advocacy of their claims".[9] A case of damning by faint praise if ever there was one!

What lay behind this already successful physician, his commitment to anaesthesia and his involvement with the ensuing controversy over its use? Fundamentally he was a humane man who believed the object of the medical practitioner to be "the alleviation of human suffering and the preservation of human life". This lead him to try and improve the lot of his patients, whether by attempting to decrease postoperative inflammation or providing analgesia during labour. Fortunately, and unlike many physicians, he had the imagination to perceive that improvements in medical care could be made, and the forceful personality required to initiate them. His greatest achievement must be publicizing anaesthesia and challenging opponents so that it became accepted; 150 yr on it is impossible to imagine anyone having a career with so many different facets and achieving so much. Not only did he also have a happy family life, but he even found time to be a successful amateur archaeologist, becoming President of the Society of Antiquaries of Scotland in 1861.[1] It seems very likely that if James Young Simpson were alive today he would be at the forefront of progress and development while still making time for, and enjoying, his family and private life.

S. M. Rae
J. A. W. Wildsmith
University Department of Anaesthesia
Ninewells Hospital and Medical School
Dundee DD1 9SY

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Virtually all of the academic papers published by Simpson were collected together into two volumes edited by his son, Walter, and published in 1871 by Black of Edinburgh. Volume one contains his papers on obstetrics and gynaecology, and volume two his publications on anaesthesia, pain relief and hospitalization. All references relating to anaesthesia that are not specifically referenced in the text are found in this second volume. We also refer specifically to·

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EDITORIAL II

Propofol in paediatric intensive care

The need for sedation in paediatric intensive care is well recognized, both for spontaneously breathing children and those undergoing mechanical ventilation, with or without neuromuscular blocking agents. The level of sedation required varies with the pathology, but a survey of paediatric intensive care units in the UK in 1991, published in 1993, showed that most respondents favoured i.v. infusion as the method of choice for drug delivery.[1] Although a wide variety of sedative and analgesic agents have been used, reliance has traditionally been placed on opioid and benzodiazepine drugs. These have several disadvantages, including prolonged action and acute withdrawal symptoms. Almost none of the agents commonly used in adult intensive care is licensed for long-term infusion in children. Isoflurane has been used in some units, although it is expensive, its use requires the installation of scavenging facilities and concerns remain about fluoride toxicity.

After successful use in adults, the first case report describing an infusion of propofol for paediatric sedation appeared in 1987 with further reports appearing shortly afterward.[2–4] After these initial reports, the technique became increasingly popular despite the fact that propofol was not licensed for use in this situation. Although early reports suggested that infusion rates of less than 50 μg kg^{-1} min^{-1} gave acceptable sedation with rapid recovery and no undesirable side effects, almost all subsequent investigators have used much higher doses than those recommended in adults (1–4 mg kg^{-1} h^{-1}).

Reports of serious complications began to appear in the early 1990s, and appear to fall into two distinct categories. There have been several reports of signs of central nervous system irritability on withdrawal of propofol,[5–7] similar signs having been reported previously with midazolam and fentanyl.[8] More seriously, the Danish Side Effects Committee drew attention to the death of a 2-yr-old child with croup who developed hypotension, hepatomegaly and multi-organ failure after administration of propofol 10 mg kg^{-1} h^{-1} for 4 days.[9] In 1992, Parke and colleagues reported five deaths in children who had received propofol infusions lasting several days during intensive care for upper respiratory tract infections.[10] All children developed lipaemic serum, severe metabolic acidosis, hepatomegaly and multi-organ failure. After these reports, the Committee on Safety of Medicines in the UK issued a serious adverse effects warning which led to the virtual abandonment of propofol as a sedative in most paediatric intensive care units in the UK. However, two deaths were reported in Norway,[11] and five similar cases have been reported throughout the world.[12–16] Pulmonary hypertension and rhabdomyolysis have also been reported.[17] In all cases maximum infusion rates exceeded 6 mg kg^{-1} h^{-1}, and all deaths except one occurred in patients with respiratory infection. Even this child had radiographic evidence of atelectasis and tracheal secretions grew *Haemophilus influenzae.* As she had been receiving large doses of steroids for 36 h before developing metabolic acidosis, septic shock cannot be excluded.[15]

Several possible mechanisms have been suggested for these deaths, including extrinsic bacterial contamination of propofol or hypertriglyceridaemia in the presence of impaired lipid metabolism. There is clear evidence that children receiving parenteral nutrition are at an increased risk of infection,[18] possibly as a result of increased microbial translocation of intestinal micro-organisms, although in almost all cases this is associated with cholestasis and increased serum bilirubin concentration.[19] Another suggestion is that some host factor may be responsible by the inclusion of viral DNA into an already susceptible genotype. Some have drawn attention to the similarities to the changes seen in malignant hyperthermia and Reye's syndrome.

Although the case reports and adverse effects warnings have undoubtedly had a significant impact throughout the world, propofol is still being used extensively for intensive care sedation in children, especially in North America. The published literature describes its use in more than 300 children from less than 1 to 12 yr of age for periods of up to 2 weeks with infusion rates, where stated, of 0.44–26.3 mg kg^{-1} h^{-1} without serious side effects. It appears to be used in almost all of the 144 paediatric intensive care units in the USA, particularly during weaning from ventilatory support or during transition from sedation with other drugs to awareness. It is also used in children with head injuries who require periodic awakening for assessment. Although many centres restrict its use to periods of up to 48 h or limit the amount of propofol infused, in others no such restrictions are applied. Reed and Blumer in Cleveland have challenged the causal relationship between propofol administration and the development of metabolic acidosis,[20] and have used the drug in more than 500 cases without serious complications. They have also used propofol continuously for up to 3 months. Surprisingly, the United States Food and Drugs Authority has issued no warning about its use and in fact its Advisory Committee on Anaesthetic and Life Support Drugs stated in 1992 that "propofol has no direct link to paediatric deaths in hospital intensive care units and no identifiable cardiac adverse events in children and adults". The manufacturers however issued a warning against its use for continuous sedation of paediatric intensive care patients.

In an article published in this issue of the *British Journal of Anaesthesia,* Martin, Murthy and Petros[21] have revisited this difficult issue. Their study investigated the metabolic, biochemical and haemodynamic effects of propofol infusion (up to 4 mg kg^{-1} h^{-1}) in nine sedated children studied for 48 h after cardiac surgery. The children's lungs were ventilated to mild hypocapnia, had no evidence of respiratory tract infections and were not receiving parenteral nutrition containing additional Intralipid. There was no evidence of metabolic acidosis or significant alterations in serum urea, creatinine, glucose or triglyceride concentrations from baseline values. Liver enzymes did not increase significantly during this period and no ketones were detected in urine. The authors concluded that propofol infusions can be used safely in postoperative cardiac patients if strict guidelines are followed, and they support the call for properly conducted clinical studies to re-evaluate its use in paediatric intensive care. Review of the published literature would suggest that children with existing sepsis or primary respiratory problems should probably be excluded from such research, and that infusion rates should be kept to those used in adults, even if other drugs have to be used to ensure adequate sedation. Large studies are required before criteria for the safe use of propofol in paediatric intensive care can be defined.

D. J. HATCH
Portex Department of Anaesthesia
Institute of Child Health
London

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British Journal of Anaesthesia 1997; 79: 276–279

CLINICAL INVESTIGATIONS

Metabolic, biochemical and haemodynamic effects of infusion of propofol for long-term sedation of children undergoing intensive care

P. H. MARTIN, B. V. S. MURTHY AND A. J. PETROS

Summary

We have studied prospectively, in nine children requiring sedation to facilitate mechanical ventilation, the metabolic, biochemical and haemodynamic effects of infusion of propofol. Children were given infusions of propofol 1–4 mg kg^{-1} h^{-1} and fentanyl 1–5 μg kg^{-1} h^{-1} for 48 h. Heart rate, arterial pressure, central venous pressure, fluid balance and urine output were recorded hourly and sedation scores every 4 h. In addition to routine haemodynamic and biochemical measurements in the intensive care, 6-hourly arterial blood-gas analysis and 12-hourly measurements of serum concentrations of glucose, lactate and electrolytes, renal function, triglycerides and liver function tests were performed. Urine was analysed for ketones. There were no significant differences in haemodynamic or biochemical variables during the 48-h period. In this small sample of children, propofol combined with fentanyl provided excellent sedation with no evidence of cardiac, renal or hepatic impairment. Under these very proscriptive conditions we did not encounter lipaemia or acidosis with infusion of propofol. Thus propofol may be a safe sedative agent for use in paediatric intensive care if used appropriately. Further large scale studies are needed to determine if warnings against the use of this agent in paediatric intensive care units are justified. (*Br. J. Anaesth.* 1997; **79**: 276–279).

Key words
Anaesthetics i.v., propofol. Sedation Intensive care, sedation. Anaesthesia, paediatric.

As the use of propofol becomes more widespread in adult intensive care units,[1 2] the reported deaths of seven children[3–5] who received propofol for sedation as part of their intensive care management is of considerable concern. The children aged between 4 weeks and 9 yr who required mechanical ventilation for severe upper respiratory tract infections developed lipaemia and metabolic acidosis before death. Although no causal relationship was established, the Committee on Safety of Medicines issued a serious adverse effects warning leading to the immediate abandonment of propofol as a sedative agent in the paediatric intensive care unit.[6]

The aim of this open prospective study was to investigate the effects of a sedative infusion regimen of propofol on the metabolic, biochemical and haemodynamic changes in a group of children without upper respiratory tract infections over a 48-h period. Propofol was used in combination with fentanyl at low doses and under very specific conditions to facilitate ventilation in a group of children in a cardiac surgical intensive care unit for a predetermined period.

Patients and methods

This study was approved by the Ethics Committee of the Royal Liverpool Children's NHS Trust. Parents were fully informed of the current concerns about the use of propofol in children. They were also made aware of the case report of the five deaths and given an information sheet describing these issues in simple terms. An Exemption from Licences of the Medicine Special Cases and Miscellaneous Provisions Order 1972 was also obtained from the Medicines Control Agency.

Nine child needing sedation to facilitate mechanical ventilation after cardiac surgery or weaning from ventilation were considered eligible for the study. Mean arterial pressure was monitored invasively via an indwelling arterial cannula in all children, and in five children central venous pressure was monitored. Concurrent sedatives were stopped and infusions of propofol 1–4 mg kg^{-1} h^{-1} and fentanyl 1–5 μg kg^{-1} h^{-1} were commenced without loading boluses. Neuromuscular blocking agents were not given. Sedation was scored every 4 h.[7] Bolus doses of propofol and fentanyl, equivalent to 25% of the current hourly infusion rate, were given during interventions such as tracheal suctioning or physiotherapy. Propofol was continued for 48 h or until the child was considered ready for tracheal extubation, if sooner. The lungs were ventilated to mild hypocapnia with oxygen-enriched air and inotropic support was continued according to clinical requirements. Heart rate, arterial pressure, central venous pressure, fluid

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P. H. MARTIN, FRCA, B V. S. MURTHY, MD, FFARCSI, MMEDSC, A. J. PETROS*, FFARCSI, Cardiac Intensive Care Unit, Royal Liverpool Children's NHS Trust, Alder Hey, Eaton Road, Liverpool L12 2AP. Accepted for publication: April 11, 1997.

*Present address for correspondence: Paediatric Intensive Care Unit, Great Ormond Street Hospital for Children NHS Trust, London WC1N 3JH.

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input and urine output were recorded hourly. Parenteral nutrition containing Intralipid was avoided. In addition to hourly cardiovascular and respiratory observations made in the ICU, 6-hourly arterial blood-gas analysis and 12-hourly measurements of serum concentrations of electrolytes, urea, creatinine, glucose, lactate, triglycerides, total bilirubin, γ-glutamyltransferase (GGT), aspartate aminotransferase (AST), alanine aminotransferase (ALT) and alkaline phosphatase were made (Axon Clinical Chemistry Analyser, Bayer Diagnostics, UK).[8] Age specific normal ranges generated within our laboratory were used for comparisons. Urine was collected 12-hourly and analysed for ketones and organic acids.

Statistical analysis was performed using the Kruskal–Wallis non-parametric ANOVA test. All values are expressed as mean (95% confidence interval (CI)). $P<0.05$ was considered statistically significant.

Results

Nine children (four males) completed the study. One child required a second episode of ventilation, 2 months later, after developing left upper lobe pulmonary consolidation resulting in 10 episodes of propofol infusion. Median age was 19 months (95% CI 2.2–104.7 months) and mean weight 13.9 (2.8–25.0) kg. The trachea of one child was extubated within 24 h and in two children, propofol infusion was continued for clinical reasons for 84 h and 144 h with no adverse effects. Five children with Down's syndrome had atrioventricular septal defect (AVSD) repair, three had complete repair of tetralogy of Fallot and one had a tracheal stent insertion for tracheomalacia. The mean dose of propofol infusion was 2.1 (1.5–2.8) mg kg^{-1} h^{-1} and mean duration of infusion was 35.3 (33–87) h.

SEDATION

All children were considered adequately sedated. Mean baseline sedation score was 4.2 (1.3–3.2), and was 4.25 (3.3–5.2) at 12 h, 4.0 (3.2–4.9) at 24 h, 3.0 (2.4–3.6) at 36 h and 3.2 (2.4–4.0) at 48 h. There was no significant difference in sedation scores during the 48-h study compared with baseline recordings. No child required additional sedative or neuromuscular blocking agents.

CARDIOVASCULAR EFFECTS

During the 48 h of the propofol infusion there were no significant changes in heart rate, mean arterial pressure or central venous pressure. Mean baseline heart rate was 120 (94–167) beat min^{-1}, and 123 (99–160) beat min^{-1} at 12 h, 116 (89–158) beat min^{-1} at 24 h, 128 (107–155) beat min^{-1} at 36 h and 131(115–149) beat min^{-1} at 48 h. Mean baseline arterial pressure was 53 (35–73) mm Hg, and 55 (31–71) mm Hg at 12 h, 56 (49–68) mm Hg at 24 h, 56 (40–72) mm Hg at 36 h and 61 (41–80) mm Hg at 48 h. Mean baseline central venous pressure was 7 (4–9) mm Hg, and 7 (4–10) mm Hg at 12 h, 6 (4–7) mm Hg at 24 h, 7 (4–9) mm Hg at 36 h and 6 (4–7) mm Hg at 48 h. No arrhythmias were noted and in particular no episodes of bradycardia.

METABOLIC AND BIOCHEMICAL EFFECTS (TABLE 1).

Based on a mean infusion rate of 2.1 mg kg^{-1} h^{-1}, mean total lipid load provided by the 10% Intralipid emulsion in which propofol is suspended was 0.45G lipid kg^{-1} day^{-1}. No gross lipaemia was observed on direct visual inspection in any of the blood samples obtained. Although serum triglyceride concentrations were increased above the normal range quoted for our laboratory at 12 h, 24 h and 36 h, there were

Table 1 Metabolic and biochemical changes during the 48-h infusion of propofol (mean (95% confidence interval)). There were no significant differences in any variable at any time during the study. (Nine children were studied but one child was sedated twice, separated by a period of 2 months, making 10 clinical episodes)

Variables (normal range)	Baseline (n=10)	12 h (n=10)	24h (n=9)	36h (n=9)	48h (n=9)
pH	7.44	7.42	7.40	7.42	7.42
(7.35–7.45)	(7.30–7.49)	(7.38–7.47)	(7.36–7.44)	(7.39–7.45)	(7.39–7.46)
Bicarbonate	27.4	26.8	27.6	26.0	28.2
(18–29 mmol litre^{-1})	(24.0–30.7)	(24.6–28.9)	(25.0–30.1)	(24.2–27.7)	(25.6–30.9)
Base excess	+3.1	+3.6	+3.8	+1.8	+3.7
(−2.0 to +2.0)	(−0.2 to +6.4)	(+0.5 to 6.6)	(+0.7 to 6.8)	(+0.1 to 3.5)	(+1.2 to 6.1)
Lactate	1.37	1.23	1.75	1.37	1.78
(0.7–2.1 mmol litre^{-1})	(0.74–1.99)	(0.66–1.81)	(0.86–2.64)	(0.47–2.31)	(0.63–2.92)
Triglyceride	1.48	2.27	1.95	2.09	1.45
(0–1.6 mmol litre^{-1})	(0.68–2.30)	(0.17–4.40)	(1.09–2.80)	(1.07–3 10)	(0.86–2.05)
Bilirubin	11.1	19.2	17.1	18.0	18.8
(<15 μmol litre^{-1})	(4.6–17.6)	(4.7–43.0)	(2.0–37.0)	(1.7–34.0)	(2.3–40.0)
GGT	11.5	11.0	9.0	11.0	13.0
(<45 iu litre^{-1})	(3.3–19.7)	(2.3–24.8)	(3.5–14.5)	(1.0–23.0)	(4.2–30.0)
AST	36.1	40.0	39.1	41.5	47.7
(15–58 iu litre^{-1})	(24.5–47.8)	(7.9–62.0)	(16.4–61.9)	(18.9–64.1)	(20.2–75.1)
ALT	25.6	16.5	22.3	18.5	26.0
(9–36 iu litre^{-1})	(4.7–46.5)	(11.2–21.8)	(3.4–41.1)	(8.3–28.7)	(8.0–51.1)
Alkaline phosphatase	362	371	393	336	430
(187–1197 iu litre^{-1})	(173–551)	(183–440)	(224–561)	(221–450)	(224–635)

no significant differences from baseline. There was no evidence of lactic acidosis within the 48-h period, with the highest mean value of 1.78 mmol litre^{-1} occurring at 48 h. There were no significant changes in pH, bicarbonate or base deficit which remained positive throughout the period of infusion. Plasma concentrations of urea and creatinine did not change significantly from baseline, in common with serum glucose concentrations. The hepatic enzymes, AST, ALT and GGT did not increase significantly during the 48 h. No ketones were detected in any of the urine samples.

Discussion

Adequate sedation and analgesia is an integral part of intensive care management. Infusions of midazolam, propofol, fentanyl and alfentanil are used commonly in adult intensive care. However, the last available survey in 1991 of PICU in the UK revealed that at that time the majority were using these sedatives outside their product licenses.[9]

The pharmacodynamics and pharmacokinetics of propofol make it ideal for maintenance of prolonged sedation of patients undergoing mechanical ventilation in the ICU. Propofol has been studied extensively in adult intensive care, where it has been shown to provide satisfactory sedation and rapid recovery with minimal side effects.[10–13] In contrast, there is little published information on the clinical use of propofol in critically ill children.[14 15] The case report of five deaths in children with upper respiratory tract infections described propofol infusions at concentrations varying from 4 mg kg^{-1} h^{-1} to a short maximum rate of 13.6 mg kg^{-1} h^{-1} for 8 h.[3] Even for this relatively short period, the equivalent infusion rate for a 70-kg adult would be 95.2 ml h^{-1} giving a total volume of 762 ml in the 8-h period. The doses used in our study (mean 2.1 mg kg^{-1} h^{-1}) were much lower and equivalent to approximately 15 ml h^{-1} for a 70-kg adult, which is a more generally acceptable rate of infusion used in adult intensive care. Parke and colleagues[3] acknowledge that propofol contains 0.1 g of lipid per millilitre and that 10% Intralipid from the propofol infusion might have contributed to the deaths. They calculated that even at the maximum rates of propofol infusion used, less than half of the recommended infusion rate of 10% Intralipid in infants was given (Intralipid data sheet, Pharmacia, Milton Keynes, UK) and therefore the lipid content of propofol was unlikely to be the sole cause of the deaths. However, it is not clear if the five infants also had supplementary parenteral nutrition and how much Intralipid was prescribed in addition to that received from the propofol infusion. As lipid metabolism may be impaired in children with sepsis, the authors were correct in observing that added lipid load from propofol may have contributed to the lipaemic serum noted. They were also correct to point out that infusions of lipid should be minimized and triglyceride concentrations monitored carefully in septic children.

Several other case reports suggest that there may be a syndrome of propofol associated metabolic acidosis (PAMA) which is idiosyncratic in incidence. The syndrome appears to include metabolic acidosis, hypercapnia and hyperthermia, resulting in hypotension unresponsive to vasopressors and broad complex bradycardia unresponsive to chronotropes or mechanical pacing.[5] This has led some to speculate that this syndrome is similar to that of malignant hyperthermia.[16] The picture of a previously healthy child admitted with a trivial URTI or minor neurological symptoms who suddenly and unexpectedly dies after administration of a specific agent has led others to draw similarities with the discovery of aspirin producing Reye's syndrome in children. Unfortunately, there are no data available in terms of number of patient days over which propofol was infused to allow an estimate of the incidence of PAMA and there are still many unanswered questions. If PAMA is an idiosyncratic response why is it seen only in children receiving infusions and not in those who receive propofol for induction of anaesthesia? All the reports of PAMA are in infants and young children; is this a maturational problem in relation to lipid load? Why is PAMA not seen in adults receiving infusion of propofol; is it being missed because deaths from cardiac arrhythmias are more explicable in an adult population?

In 1992 the United States Food and Drugs Authority advisory committee (Anesthetic and Life Support Drugs) concluded that propofol has no direct link to paediatric deaths in hospital intensive care units and no identifiable link to adverse cardiac events in children and adults[17]. A recent study in 28 children has defined the pharmacokinetics of propofol and recommended a dose regimen to maintain optimal sedation which requires a serum concentrations of 1 mg litre^{-1}. The regimen varies with time, starting at infusion rates of 7.5 mg kg^{-1} h^{-1} and decreasing to 4.3 mg kg^{-1} h^{-1} over 4 h.[18] We recommend a much lower dose of 2.1 mg kg^{-1} h^{-1}. This difference in dose rates probably results from our concomitant use of an opioid, which contributed to lower propofol requirements. When used under the specifically controlled circumstances such as those we have described in appropriately monitored and resuscitated children, we believe that propofol sedation has a valuable role in paediatric intensive care. In our practice we have found propofol to be particularly useful in allowing rapid changes in sedation levels and so facilitating ventilation and weaning. Although we have studied only a small number of children we could find no evidence of progressive acidosis or significant metabolic or biochemical derangements.

We have demonstrated that in this small group of children without respiratory disease and not receiving parenteral nutrition, sedation with propofol caused no significant haemodynamic, metabolic or biochemical changes. In no instance did the infusion rate have to be reduced from that dictated by the study design because of adverse haemodynamic effects. No significant changes in blood lactate concentrations occurred, indicating adequate tissue oxygenation. Our findings support those of a similar study in 10 critically ill adults receiving propofol infusions (2–4 mg kg^{-1} h^{-1}). No significant changes in global oxygen transport and delivery, lactate concentration and cardiac output were noted, and there was no evidence of lipaemia or triglyceridaemia,[13] although the adult liver may be better able to handle lipids in sepsis.

We conclude that propofol may be used in post-operative cardiac patients in the doses recommended and in combination with an opioid. We found that propofol was useful in sedating children with Down's syndrome who are often confused on emerging from sedation. We agree with those who request correctly conducted clinical studies to re-evaluate the use of propofol infusions in children.[15] However, despite enthusiasts such as Reed and Blumer declaring, "propofol bashing: the time to stop is now"[19] we still have several reservations about its indiscriminate use in sick children. We recommend that until more information is available on the incidence of PAMA and its precipitating factors, propofol should not be administered to children who are suffering from an acute infective process, particularly an upper respiratory tract infection; it should not be used as the sole sedative agent; it should not be infused at greater than 5 mg kg^{-1} h^{-1}; and its continued use should be reviewed daily.

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Comparison of sevoflurane and halothane for outpatient dental anaesthesia in children

S. T. PARIS, M. CAFFERKEY, M. TARLING, P. HANCOCK, P. M. YATE AND P. J. FLYNN

Summary

In a prospective, randomized, double-blind clinical study, we have studied 100 children, aged 2–12 yr, to compare halothane and sevoflurane in outpatient dental anaesthesia. All patients were unpremedicated and received inhalation induction using nitrous oxide in oxygen supplemented with either halothane (maximum inspired concentration 5%) or sevoflurane (maximum inspired concentration 8%). Time to loss of the eyelash reflex was more rapid using sevoflurane although time to adequate anaesthesia (to allow insertion of a mouth prop) was slower in the sevoflurane group. The incidence of cardiac arrhythmia was higher during halothane (62%) than during sevoflurane anaesthesia (28%) ($P<0.005$) and the arrhythmias were more often ventricular in origin. The two agents were comparable in terms of ease of use and quality of anaesthesia, and times to eye opening and satisfying discharge criteria were similar. We conclude that sevoflurane has qualities that have made halothane the most used inhalation agent for children, and that it is superior to halothane in dental outpatients where cardiac arrhythmias are a particular problem. (*Br. J. Anaesth.* 1997; **79**: 280–284).

Key words
Anaesthetics volatile, halothane. Anaesthetics volatile, sevoflurane. Surgery, dental. Children.

It is becoming increasingly apparent that sevoflurane has the potential to be the inhalation induction agent of choice in children.[1–4] It is relatively pleasant smelling, non-irritant and has a rapid onset and offset of action by virtue of its low blood-gas solubility.

Halothane is still used widely in paediatric dental outpatient anaesthesia as it is relatively non-pungent and provides smooth induction and recovery. Its main disadvantages are a strong odour, cardiovascular depression, a propensity to cause arrhythmias and rarely hepatic necrosis, especially after repeated exposures. During dental surgery, the incidence of arrhythmia during halothane anaesthesia has been reported to be as high as 75%.[5] The use of enflurane or isoflurane reduces the incidence of arrhythmias during oral surgery but both are inferior to halothane in terms of ease of induction and quality of anaesthesia.[5–7] This study was designed to compare the incidence and type of arrhythmia, and quality of anaesthesia and recovery during sevoflurane and halothane anaesthesia in children undergoing outpatient dental extraction.

Patients and methods

After obtaining Ethics Committee approval and written parental consent, we studied 100 unpremedicated children, ASA I–II, aged 2–12 yr, undergoing outpatient dental extractions under general anaesthesia; patients were allocated randomly to one of two groups to receive either sevoflurane or halothane.

Electrocardiographic limb leads were attached to the patient before induction of anaesthesia and a continuous record of lead II was obtained together with a visual oscilloscope display. A paediatric pulse oximetry probe was applied before induction of anaesthesia and oxygen saturation (Sp_{O_2}) was monitored continuously throughout surgery and during recovery from anaesthesia. Arterial pressure readings before and after induction were obtained whenever possible and recorded. The time of induction, placement of the mouth prop, dental extractions and discontinuation of anaesthetic were recorded by a blinded observer who also assessed the incidence of complications during anaesthesia and recovery. Complications were graded on a scale from 0 to 3: 0=not present; 1=present but not troublesome; 2=causing interference with technique or requiring treatment; 3=so troublesome that technique had to be abandoned or patient needed admission to hospital. Complications assessed were intolerance to the vapour, breath-holding, coughing, salivation, laryngospasm, vomiting, Sp_{O_2} <90%, rigidity, excitatory movements and shivering. In the recovery area, times to eye opening to command and to "street fitness" (able to drink and walk around the recovery area unaided) were also recorded.

Dental extractions were carried out in the supine position and anaesthesia was administered by one

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S. T. PARIS, BSC, MB, BS, FRCA, M. TARLING, SRN, BSC, MSC, P. HANCOCK, BSC, P. J. FLYNN, MB, BCH, FFARCSI, FRCA (Anaesthetics Unit); M. CAFFERKEY, MB, CHB, MRCP (Department of Medicine); P. M. YATE, MB, FRCA (Anaesthetics Department); Royal Hospitals NHS Trust, Whitechapel, London E1 1BB.
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Table 1 Patient characteristics and clinical data (median (95% central range) or number of patients)

	Sevoflurane (n=50)	Halothane (n=50)
Age (yr)	5 (2–11.5)	5 (2.3–9.7)
Weight (kg)	19 (12–48.9)	18 (7–42)
Sex (M/F)	29/21	31/19
Race (Asian/Caucasian/Negroid)	23/22/5	22/20/8
Cooperative at induction	38	41
Un-cooperative at induction	12	9
Extent of surgery (n)		
Ant. extractions only	7	8
Post. extractions only	31	31
Both ant.and post.extractions	12	11
Duration of surgery (min)	2.53 (0.3–9.2)	1.91 (0.4–9.9)
Duration of anaesthesia (min)	6.72 (2.5–12.8)	5.58 (2.9–13.7)

of three consultant anaesthetists with extensive experience of the technique. Anaesthesia was induced by inhalation of 50% nitrous oxide in oxygen with the selected vapour introduced in increments of 1% to a maximum of 5% halothane, and in increments of 2% to a maximum of 8% sevoflurane. The concentration of the agents was increased every 3–5 breaths or more rapidly if tolerated by the patient. Sevoflurane and halothane were administered via recently calibrated vaporizers (Blease-Datum, TEC 3 Ohmeda). The vapour was delivered by a Bain system with the anaesthetist holding the patient end of the system as close to the child's face as possible. Fresh gas flow rates were always in excess of 200 ml kg^{-1} min^{-1}. When the child lost consciousness, a nasal mask was applied and anaesthesia was maintained with 50% nitrous oxide in oxygen and the selected vapour. Maintenance concentrations of sevoflurane were 2–4% and 1–2 % for halothane. Anaesthetic gases were discontinued at the time of extraction of the penultimate tooth. The child was given 100% oxygen and at completion of the procedure was turned to the left lateral, head-down position. Transfer to the recovery area occurred when the patient had a patent airway, acceptable respiratory pattern and normal oxygen saturation, and any cardiac arrhythmia had resolved.

ECG recordings were analysed by a physician who was unaware of the anaesthetic agent used. These were analysed over three times: induction (time from gases on to commencement of surgery), surgery (end of induction to discontinuation of nitrous oxide and anaesthetic vapour) and recovery (end of surgery to discharge from the operating theatre).

Data are presented as mean (SD) or median (95% central ranges) unless otherwise stated. Statistical analyses were performed using the Mann–Whitney *U* test, Fisher's exact test or the chi-square analysis, as appropriate. $P<0.05$ was considered statistically significant.

Results

Data from 100 children (50 in each treatment group) were collected and analysed. Patient characteristics and clinical data, including duration of anaesthesia and surgery, and extent of surgery, were similar in the two groups (table 1). No patient was excluded during the study.

HEART RATE AND ARTERIAL PRESSURE

The incidence of heart rate decreasing to less than 80 beat min^{-1} was similar in both groups (sevoflurane group 16%, halothane group 14%) and no patient required treatment. Mean maximum heart rate was significantly higher in the sevoflurane group (146 beat min^{-1}) than in the halothane group (138 beat min^{-1}) (P=0.019).

It was possible to obtain systolic arterial pressure measurements before and after induction of anaesthesia in 75 patients. In the sevoflurane group there was a mean decrease of 1.6 (SD 17.7) mm Hg; in the halothane group there was a mean decrease of 9.4 (17.7) mm Hg. This difference was not statistically significant (P=0.061).

ARRHYTHMIAS

All arrhythmias (table 2)

The overall incidence of arrhythmia was significantly greater in the halothane group (62% *vs* 28%) (P<0.0005). During induction, more patients in the halothane group had arrhythmias, although this difference was not statistically significant. During surgery, 44% of patients anaesthetized with halothane had arrhythmias compared with 24% given sevoflurane (P=0.035), whereas during the initial recovery period the values were 30% and 6%, respectively (P=0.002).

Supraventricular arrhythmias

The incidence of premature atrial beats and AV junctional rhythm did not differ significantly between the two groups (table 3).

Ventricular arrhythmias.

Single premature ventricular beats (PVB) occurred in 25 patients in the halothane group and in 11

Table 2 Incidence of arrhythmia during anaesthesia

	Throughout	Induction	Surgery	Recovery
Halothane (%)	62	20	44	30
Sevoflurane (%)	28	10	24	6
P	<0.0005	0.161	0.035	0.002

Table 3 Classification and incidence of arrhythmias observed. Data are number of patients in whom the arrhythmia was seen. (PVB=Premature ventricular beats)

	Sevoflurane (n=50)	Halothane (n=50)	P
Premature atrial beats	5	7	0.538
AV junctional rhythm	2	6	0.269
Occasional PVB	11	25	0.004
Bigeminy	0	15	<0.0005
Episodes of PVB <10 beats	3	11	0.021
Episodes of PVB >10 beats	0	2	0.153
Ventricular tachycardia	0	1	0.315

patients in the sevoflurane group (P=0.004). Bigeminy occurred only in the halothane group, in 15 patients (P<0.0005).

Eleven patients anaesthetized with halothane had episodes of multifocal ventricular ectopics which occurred during all three phases of anaesthesia. This arrhythmia occurred in only three patients in the sevoflurane group (P=0.021) (table 3), and in each case the episode of PVB was not longer than 4 beats. In the halothane group two patients had episodes of PVB of more than 10 beats and one patient had three episodes of ventricular tachycardia which were self-terminating.

QUALITY OF ANAESTHESIA

The technique did not have to be abandoned in any patient and therefore grade 3 of the complication score was not included in the statistical analysis.

Induction and recovery times (table 4)

The time between start of induction and loss of eyelash reflex was significantly shorter in the sevoflurane group (mean 1.5 (SD 0.6) min) compared with the halothane group (1.9 (0.5) min). However, time to insertion of the mouth prop was significantly slower after induction with sevoflurane (3.9 (1.3) min in the sevoflurane group *vs* 3.5 (0.7) min in the halothane group).

In the recovery period, times to eye opening and discharge were similar in both groups (table 4).

Table 4 Induction and recovery times for sevoflurane and halothane anaesthesia. Data are mean (SD)

	Induction (time (min) from gases on)		Recovery (time (min) from gases off)	
	Loss of eyelash reflex	Insertion of mouth prop	Eye opening	Fit for discharge
Sevoflurane (n=50)	1.5 (0.6)	3.9 (1.3)	7.3 (2.3)	23.0 (5.6)
Halothane (n=50)	1.9 (0.5)	3.5 (0.7)	7.8 (2.9)	23.2 (5.4)
P	0.0003	0.04	0.325	0.875

Table 5 Quality of anaesthesia in the sevoflurane (Sevo.) and halothane (Hal.) groups. Data are number of patients, with complications scored 0–2 according to severity

		Induction			Surgery			Recovery		
Complication	Grade	Sevo. (n=50)	Hal. (n=50)	P	Sevo. (n=50)	Hal. (n=50)	P	Sevo. (n=50)	Hal. (n=50)	P
Intolerance	0	32	36	0.52	—	—		—	—	
	1	15	9		—	—		—	—	
	2	3	5		—	—		—	—	
Coughing	0	43	45	0.54	48	50	0.16	44	46	0.51
	1	7	4		2	0		6	4	
	2	0	1		0	0		0	0	
Salivation	0	47	49	0.99	50	50	—	50	50	—
	1	3	0		0	0		0	0	
	2	0	1		0	0		0	0	
Laryngospasm	0	47	49	0.32	49	48	0.55	49	50	0.32
	1	2	0		1	1		0	0	
	2	1	1		0	1		1	0	
Vomiting	0	50	50	—	50	50	—	48	47	0.65
	1	0	0		0	0		2	3	
	2	0	0		0	0		0	0	
Breath-holding	0	49	46	0.17	50	49	0.32	50	50	—
	1	1	3		0	1		0	0	
	2	0	1		0	0		0	0	
Sp_{O_2}<90	0	50	49	0.32	49	49	—	50	50	—
	1	0	0		0	0		0	0	
	2	0	1		1	1		0	0	
Rigidity	0	41	48	0.026	48	49	0.55	48	50	0.16
	1	9	2		1	1		0	0	
	2	0	0		1	0		2	0	
Movement	0	17	17	0.70	45	43	0.54	23	32	0.044
	1	29	26		5	7		17	14	
	2	4	7		0	0		10	4	
Shivering	0	—	—		—	—		50	49	0.32
	1	—	—		—	—		0	1	
	2	—	—		—	—		0	0	

Complications

The incidences of intolerance, airway reflex responses, hypoxaemia (Sp_{O_2} <90%), vomiting and shivering were similar between the two groups.

Nine patients in the sevoflurane group demonstrated rigidity during induction compared with two in the halothane group (*P*=0.026), but this was not severe enough to interfere with the technique (table 5).

During the recovery period, the incidence of excitatory movements on emergence was significantly higher in the sevoflurane group (*P*=0.038).

Discussion

Inhalation anaesthesia is used widely for induction in paediatric outpatient dental surgery. Halothane is still the agent favoured by most anaesthetists in this clinical situation, but its main problems are its propensity to cause cardiac arrhythmia, and the risk, albeit rare, of fulminant hepatitis on repeated exposure. The incidence of arrhythmia in patients undergoing dental surgery during halothane anaesthesia has been reported as high (75%).[8] In our study we found that 62% of patients had arrhythmias during anaesthesia with halothane compared with only 26% of patients given sevoflurane.

The significance of arrhythmias during anaesthesia for oral surgery with respect to anaesthetic mortality has yet to be established. However, the incidence of unexplained deaths in dental anaesthetic mortality reports[9 10] and evidence from recent coroners' inquests suggest that they cannot be ignored. In this study the incidence of arrhythmia during induction and surgery in the halothane group was approximately double that in the group receiving sevoflurane. It was notable that during the recovery period 30% of patients given halothane had arrhythmias compared with only 6% after sevoflurane. Coplans and Curson found that more than 50% of deaths associated with dentistry occurred during the recovery period.[9] Sevoflurane may offer an increased safety margin in dental anaesthesia because of its low propensity to cause arrhythmias, but also because the associated arrhythmias are predominantly supraventricular in type. Analysis of the recordings showed that ventricular arrhythmias were found almost exclusively in the group receiving halothane. While it is not known which arrhythmias associated with anaesthesia are significant, it is generally accepted that arrhythmias which are ventricular in origin carry a higher risk. The incidence of arrhythmia in association with oral surgery was found to be much lower when enflurane (10%) and isoflurane (14%) were used.[5 6] As with sevoflurane, ventricular ectopy was almost uniformly absent, but neither enflurane nor isoflurane offered equivalence in terms of facility of induction to halothane.

We found that sevoflurane and halothane were similar in terms of "smoothness" and quality of anaesthesia overall. The higher incidence of rigidity during induction with sevoflurane was not severe enough to interfere with anaesthesia. Excitatory phenomena during this phase have been reported previously with this agent.[4 11 12] Agitation and restlessness during recovery were also more frequent after sevoflurane and were noted by other investigators.[1 13] The most likely explanation is that patients are experiencing rapid emergence as the agent is eliminated rapidly.

In view of the lower blood-gas partition coefficient of sevoflurane, it would be expected to provide more rapid inhalation induction than halothane.[13–15] However, the rate of inhalation induction of anaesthesia is also determined by potency, maximum deliverable inspired concentration (limited by the vaporizer used) and the rate of increase of the inspired concentration. In our study no attempt was made to match the two groups in terms of equivalent MAC multiples of the volatile agents during induction, as in several recent comparative studies.[1 14 16 17] Within the confines of our study we confirmed that the time to loss of the eyelash reflex was indeed shorter with sevoflurane, but the time required to achieve the depth of anaesthesia that would allow insertion of a mouth prop was marginally, but significantly, longer compared with halothane. Black and co-workers[15] recently compared induction times in paediatric patients using a method similar to that described in this study and still found a shorter induction time with sevoflurane than with halothane. However, the end-point for completion of induction was the time to steady spontaneous ventilation with small pupils and central gaze. We found that these criteria did not always correspond to a plane of anaesthesia deep enough to allow insertion of a mouth prop for dental surgery. Furthermore, Sarner and colleagues[4] recently compared times to intubation during sevoflurane and halothane anaesthesia and showed that the two were almost identical. It seems that while induction of anaesthesia is more rapid with sevoflurane, the time needed to achieve deeper planes of anaesthesia is similar to that with halothane. The maximum concentrations of the agents that we could deliver were 5% halothane and 8% sevoflurane. In this age group, these correspond to approximately 5 MAC and 4 MAC, respectively; this suggests that part of the limitation of induction time for sevoflurane may be a function of the vaporizer. In addition, sevoflurane is more of a respiratory depressant than halothane at concentrations greater than 1.4 MAC,[18] so that at deeper planes of anaesthesia uptake of the vapour may be slower than halothane and this may also make induction relatively slower.

We did not find any difference in the rate of emergence and full recovery, unlike recent studies showing that recovery from sevoflurane anaesthesia was more rapid, as would be expected from its lower blood-gas solubility.[14 17 19] However, the duration of anaesthesia required for outpatient dental surgery is very short and in these circumstances halothane would not be expected to have a prolonged recovery period.

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Comparison between halothane and sevoflurane for adult vital capacity induction

J. E. HALL, T. A. OLDHAM, J. I. M. STEWART AND M. HARMER

Summary

We have examined the differences in ventilatory characteristics between halothane and sevoflurane when used for adult vital capacity induction of anaesthesia. The study was conducted in a randomized, double-blind manner. After 13 patients had been enrolled, the study was curtailed because the blinded observer thought that there was an unacceptably high incidence of adverse events. After the randomization code was revealed, the adverse events were found to be in the halothane group. Although the sample size was small, minute volumes appeared to be maintained in the sevoflurane group. Ventilatory frequencies were similar in the two groups after insertion of the laryngeal mask airway, but tidal volumes were significantly greater in the sevoflurane group (P=0.0013). (*Br. J. Anaesth.* 1997; **79**: 285–288).

Key words
Anaesthetic techniques, induction. Anaesthetics volatile, sevoflurane. Anaesthetics volatile, halothane. Ventilation, anaesthetics, effects of.

In the course of a recently completed study in which sevoflurane was used for adult gaseous induction,[1] it was noticed that the technique appeared to be associated with tachypnoea[2] of a magnitude not reported previously. Tachypnoea appeared to be responsible for very rapid deepening of anaesthesia and it was postulated that this was associated with an increase in tidal volume. If this is the case, it would appear that sevoflurane used in this way stimulates respiration at these concentrations, although this could be technique- and not agent-specific.

Although vital capacity induction has been attempted with all currently available volatile agents, including irritant agents such as isoflurane,[3] it has been studied most extensively with halothane.[4–6] This study was undertaken in adults to compare the ventilatory characteristics during high concentration gaseous induction using sevoflurane and halothane.

Patients and methods

Approval for the study was obtained from the local Research Ethics Committee. It was planned to recruit to the study 24 ASA grade I and II patients of both sexes, aged 18–65 yr, undergoing day-case orthopaedic surgery.

Exclusion crtieria were: patients receiving (either acutely or chronically) any drugs that might alter the minimum alveolar concentration of the volatile agent, those with a body mass index >1.5 times normal, those who had received halothane anaesthesia in the previous 3 months, were receiving enzyme-inducing drugs or in whom it was anticipated that large amounts of adrenaline-containing local anaesthetics would be used during operation. The study was randomized and double-blind. All observations were made by a single-blinded investigator (J. E. H.) and all inductions were performed by two anaesthetists familiar with the vital capacity induction technique (T. A. O. and J. I. M. S.). Patients were unpremedicated. The vital capacity technique was explained to patients during the preoperative visit. In the anaesthetic room, patients were allocated to one of two groups.

Group 1. Patients' lungs were preoxygenated from a Mapleson C breathing system which was supplied from a separate oxygen source in the anaesthetic room. After preoxygenation, patients were instructed to expire to residual volume. During this time the breathing system was changed to a prefilled Mapleson A breathing system with a 4-litre reservoir bag. Patients then took a vital capacity breath of the gaseous induction mixture which they held for as long as possible. When they could not hold their breath anymore, they were allowed to breathe normally. The induction mixture consisted of 8% sevoflurane (dial concentration) and 66% nitrous oxide in oxygen, with a total fresh gas flow of 6 litre min^{-1}. End-tidal volatile concentrations at the distal end of the system were measured using a Capnomac Ultima monitor (Datex, Helsinki, Finland), and filling of the Mapleson A system was commenced when the monitor indicated a concentration greater than 7.5%. Timing of induction commenced from the start of inhalation after expiration to residual volume.

J. E. HALL, MA, MB, CHB, FRCA, T. A. OLDHAM, MB, BS, FRCA, J. I M. STEWART, MB, CHB, FRCA, M. HARMER, MB, BS, FRCA, Department of Anaesthetics and Intensive Care Medicine, University of Wales College of Medicine, Heath Park, Cardiff CF4 4XN. Accepted for publication: March 25, 1997.

Correspondence to J. E. H.

Group 2. Induction proceeded as in group 1 but 4 % halothane (dial concentration) was used. Filling of the Mapleson A system commenced when the monitor indicated a concentration greater than 3.5%.

In both groups, jaw relaxation was tested every 30 s after loss of the eyelash reflex. When this was achieved, a laryngeal mask airway was inserted. Patients continued to breathe the same concentration of volatile agent for 2 min after insertion of the laryngeal mask airway, after which the anaesthetist was allowed to proceed with an anaesthetic appropriate to the surgical procedure. Any adverse airway events during induction were treated in a manner that was thought appropriate by the anaesthetist.

The vaporizer was draped. The observer wore two face masks to eliminate the smell of the volatile agents and entered the anaesthetic room only when induction was about to commence. The agent indicator and its scale on the agent monitor were covered. The observer recorded the following: (1) time from the start of induction to cessation of finger tapping; (2) time from start of induction to loss of the eyelash reflex; (3) time from start of induction to jaw relaxation and insertion of the laryngeal mask airway; (4) minute volume, ventilatory frequency and tidal volume, 1 and 2 min after insertion of the laryngeal mask airway; and (5) presence or absence of adverse airway events.

Minute volumes and ventilatory frequencies were measured using a vane type spirometer (5410 Volume Monitor, Ohmeda, Louisville, USA) which gave running total averages over the previous six breaths. Tidal volumes were calculated from these values.

Laryngospasm and breath-holding, their duration and any intervention, salivation sufficient to wet a finger, coughing and excitation were noted. Excitation was graded as: no excitation; mild, slight movement of the patient; moderate, more marked movement but insufficient to interfere with induction; and severe patient movement sufficient to disrupt the induction process.

The number of patients required for the study was calculated from observations made during an earlier study using sevoflurane in nitrous oxide and oxygen[1] during which a mean ventilatory frequency of 33 (SD 6.1) bpm was noted after insertion of the laryngeal mask airway. Data for gaseous induction with halothane were less readily available, although a pilot study showed a mean ventilatory frequency of 25 (SD 6) bpm. Thus a difference in ventilatory frequency of 8 bpm could be expected with an SD of 6 bpm, leading to a standardized difference of 1.33. Using Altman's nomogram[7] for a study with a power of 0.90, 24 patients would be needed to give a significant result at the 0.05 level.

Results

After 13 patients had been enrolled, the study was stopped because the blinded observer thought that there was an unacceptably high incidence of adverse events. The randomization code was revealed and the available data examined. Of the 13 patients, six had received halothane and seven sevoflurane inductions. Mean end-expired sevoflurane and halothane concentrations after insertion of laryngeal mask airway were 3.7 (range 3.2–4.5) % and 2.0 (1.7–2.3) %, respectively.

There was a high incidence of adverse events in the halothane group, as shown in table 1. Patient No. 11 rapidly become asystolic shortly after insertion of the laryngeal mask airway. This responded to atropine, adrenaline, intubation and DC shock at 200 J twice and then 360 J. He was found subsequently to be a drug abuser and to have a cardiac conduction defect. He made a full recovery. Patient No. 3 had atrial ectopics during induction of anaesthesia which resolved spontaneously; this patient also had a crowing laryngospasm which was treated by manual ventilation. Ventilation of the lungs did not appear to have an adverse effect on the airway in this patient as laryngospasm resolved within 30 s.

Times to cessation of finger tapping and loss of eyelash reflex were comparable in both groups although times to jaw relaxation and to being settled after insertion of the laryngeal mask airway were significantly more rapid with sevoflurane (table 2).

Comparable ventilatory frequencies were seen after insertion of the laryngeal mask airway. These were associated with high minute volumes in the sevoflurane group which were maintained over the first 2 min after insertion of the laryngeal mask airway. Large tidal volumes were sustained in this group whereas they had reduced by 2 min in the

Table 1 Patient data, and adverse events and excitation accompanying induction

Patient No./Sex (M/F)/ Age (yr)/Weight (kg)	Induction agent	Excitation	Adverse event	Intervention required
1: F 49 (65)	Sevoflurane	None	None	None
2: M 20 (74)	Sevoflurane	None	None	None
3: M 54 (96)	Halothane	None	Laryngospasm lasting 30 s	Manual ventilation
4: M 28 (85)	Halothane	Moderate	Salivation	Oral suction
5: F 19 (66)	Halothane	Severe	None	None
6: M 32 (83)	Halothane	None	Breath-holding lasting 25 s	None
7: M 34 (86)	Sevoflurane	Mild	None	None
8: F 18 (66)	Sevoflurane	None	None	None
9: F 54 (55)	Sevoflurane	None	None	None
10: F 65 (69)	Sevoflurane	None	None	None
11: M 19 (82)	Halothane	Severe	Cardiac arrest	Cardiopulmonary resuscitation
12: F 54 (78)	Sevoflurane	None	None	None
13: M 27 (73)	Halothane	None	Laryngospasm lasting 20 s	None

Table 2 Times to induction end-points. Results are (mean (SD) [range]). $^*P<0.05$, $^{**}P<0.02$

	Sevoflurane (n=7)	Halothane (n=6)
Time to cessation of finger tapping (s)	52.7 (13.5) [35–71]	68.7 (24.9) [31–105]
Time to loss of eyelash reflex (s)	68.3 (13.0) [52–83]	94.2 (47.6) [65–189]
Time to jaw relaxation (s)	125.4 (31.3) [86–182]*	205.0 (70.0) [132–317]
Time to being settled after insertion of LMA (s)	131.6 (28.5) [105–106]**	236.7 (75.6) [137–330]

Table 3 Ventilatory characteristics after insertion of the laryngeal mask airway. Results are (mean (SD) [range]). $^*P$=0.05, $^{**}P$=0.001

	Sevoflurane (n=7)	Halothane (n=5)
Ventilatory frequency after 1 min(bpm)	23.7 (5.5) [18–31]	25.2 (5.0) [18–32]
Ventilatory frequency after 2 min (bpm)	25.4 (5.7) [17–33]	29.0 (8.8) [15–37]
Minute volume after 1 min (litre min^{-1})	10.8 (5.5) [5.5–19.0]	6.2 (1.4) [4.4–8.1]
Minute volume after 2 min (litre min^{-1})	11.1 (4.0) [7.3–18.9]*	6.3 (1.4) [4.2–7.8]
Tidal volume after 1 min (ml)	451 (175) [203–679]	311 (129) [169–504]
Tidal volume after 2 min (ml)	437 (98) [263–579]**	227 (58) [158–280]

halothane group (table 3). Tidal volumes are derived values and consequently, mean tidal volume is not necessarily equal to mean minute volume divided by mean ventilatory frequency.

Discussion

Vital capacity induction was described originally using halothane[4 5] and seemed an acceptable technique. These studies were descriptive rather then comparative and indeed, no suitable comparator was available. Ruffle and colleagues' original work[4] used halothane in oxygen alone and Wilton and Thomas[5] developed the technique by adding nitrous oxide to the fresh gas flow so speeding the induction process. In this study, times to loss of eyelash reflex were similar to those achieved by Wilton and Thomas, and we used a similar technique, although the volatile concentration was not turned down after loss of the eyelash reflex.

With the introduction of sevoflurane, direct comparison with halothane was made.[8] Sevoflurane was found to be more acceptable, providing more rapid induction and reduced side effects. We observed similar findings in our study and found that sevoflurane was superior to the extent that it was necessary to curtail the study before completion. Although this was a small study, all patients who received halothane had either an adverse airway event or excessive excitation. The authors were surprised by the incidence of adverse events which was much higher than that in Wilton and Thomas's study.[5] The difference could be explained by deviation from the original description,[5] where halothane concentration was reduced from 4% to 3% after loss of eyelash and then to 2% after another 2 min. In our study we maintained halothane concentration at 4% because we wished to make a high concentration comparison with sevoflurane. Maintaining halothane at this level may have caused the increased side effects. The differing blood-gas solubilities of nitrous oxide and halothane (0.47 and 2.3, respectively) may also have contributed to the adverse events seen during halothane induction, as the less potent, less soluble nitrous oxide would have started to exert its effect first, producing a light plane of anaesthesia before halothane had its effect. The blood-gas solubilities of sevoflurane and nitrous oxide differ to a lesser extent (0.67 and 0.47, respectively). Of patients who experienced adverse events, the patient who had a cardiopulmonary arrest later admitted to illicit use of ephedrine as a performance enhancing drug and was found to have a mild intraventricular conduction defect.

Concentrations of the volatile agents used in this study have been used previously for vital capacity induction: 4% for halothane[4–6] and 8% for sevoflurane.[9] These were dial settings and the measured concentrations delivered were: greater than 3.5% halothane (4.4 minimum alveolar concentration (MAC) equivalents), and greater than 7.5% sevoflurane (3.8 MAC equivalents). These are not MAC equivalents, but the blood-gas solubility of sevoflurane (0.67) is so much less than that of halothane (2.3) that these were thought to be comparable techniques. A second gas effect from nitrous oxide may have had an influence on both induction times and respiratory characteristics. It would have had a more pronounced influence on the uptake of the more soluble gas halothane, perhaps leading to a dose-dependent effect on ventilation, although if this were the case one might then have expected some influence on induction times and this was not seen despite the higher MAC value used. The time to loss of eyelash reflex in the sevoflurane group was nearly 30% shorter than that in the halothane group, although this was not statistically significant. In a small study this is probably a type 2 error. The lack of adverse airway events during sevoflurane induction contributed to the earlier insertion of laryngeal mask airways in this group.

Ventilatory frequencies, and minute and tidal volumes were not noted before insertion of the laryngeal mask airway because of the difficulties in obtaining accurate results when holding a face mask. It was thought that jaw relaxation and laryngeal mask insertion represented a sufficiently definite end-point from which to obtain readings and that depth of anaesthesia would be comparable between the two groups at this stage. Ventilatory characteristics between the two groups appeared to be different. There is sustained hyperventilation associated with the use of high concentrations of sevoflurane. Before insertion of the laryngeal mask airway, ventilatory frequencies increased and in the sevoflurane group this was associated with tidal volumes which were sustained. One would expect a patient whose jaw is relaxed, and in whom it is possible to insert a laryngeal mask airway, to have some degree of respiratory depression. It is possible that jaw relaxation and depression of airway reflexes occur early with sevoflurane, enabling insertion of a laryngeal mask airway during hyperventilation either in the second stage or in the first plane of the third stage of anaesthesia. There may be some central stimulation of respiration before deepening of anaesthesia. Guedel, in his original description of the stages of anaesthesia,[10] noted respiration in the second stage as erratic. Guedel described respiration in the first plane of the third stage as full and rhythmic, the volume being increased; with uneventful first and second stages, the increase in volume may be approximately 25%. With eventful first and second stages, an increased carbon dioxide concentration causes respiratory volume to increase even further. Approximately 1 min after entering the third stage, respiration adjusts to moderate hyperventilation.[10] These stages were described during induction with ether with patients breathing normally and the hyperventilation described was attributed to an increase in arterial carbon dioxide tension. During vital capacity induction, greater accumulation of carbon dioxide might be expected, leading perhaps to a more pronounced effect. Tachypnoea but not hyperventilation did not occur during halothane inductions. During sevoflurane induction, respiration seemed to be regular and associated with hyperventilation. The respiratory pattern could represent either the second stage of anaesthesia in a simpler form, unaffected by the complications of airway irritation and patient movement, or the first plane of the third stage of anaesthesia. Whatever stage was present, the laryngeal mask airways were inserted at an earlier stage of anaesthesia in the sevoflurane group. The end-tidal volatile concentrations at insertion of the laryngeal mask airway would seem to support this, with the mean end-tidal sevoflurane concentration being 3.7% or 1.85 MAC and the mean end-tidal halothane 2.0% or 2.5 MAC.

The use of sevoflurane in a vital capacity induction technique was associated with sustained minute volumes, a phenomena which may be responsible in part for the rapid deepening of anaesthesia in sevoflurane vital capacity induction. Sevoflurane would appear to be superior to halothane for adult vital capacity induction when the initial halothane concentration is maintained throughout the induction period. If adult gaseous induction with halothane is to be used, then perhaps the halothane concentration should be reduced after initial loss of consciousness as in Wilton and Thomas's original description.[5]

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Laryngeal mask airway and uncuffed tracheal tubes are equally effective for low flow or closed system anaesthesia in children

D. FRÖHLICH, B. SCHWALL, W. FUNK AND J. HOBBHAHN

Summary

Low flow and closed system anaesthesia have considerable advantages in economy, limited atmospheric pollution, and maintenance of humidification and temperature. To benefit from these techniques leakage from the breathing system should be as low as possible. The sealing of the airway is crucial to ensure this. Therefore, we have investigated in 30 children, aged 2–6 yr, the effectiveness of the laryngeal mask airway (LMA) and the uncuffed tracheal tube (TT) for closed system paediatric anaesthesia, during positive pressure ventilation, in a prospective, randomized study. Ventilation was adequate in all cases with both devices. Loss of gas from the breathing system was less than 100 ml min^{-1} in 13 (87%) patients in the LMA and in 12 (80%) patients in the TT group, with a maximum of approximately 700 ml min^{-1} in the TT and approximately 350 ml min^{-1} in the LMA group. We conclude that the airway sealing with both devices was tight enough to perform low flow or closed system anaesthesia in paediatric patients aged 2–6 yr. (*Br. J. Anaesth.* 1997; **79**: 289–292).

Key words
Anaesthesia, paediatric. Equipment, anaesthesia machines. Equipment, masks anaesthesia. Ventilation, positive end-expiratory pressure. Intubation tracheal. Children.

The uncuffed tracheal tube (TT) is the established standard in paediatric airway management during anaesthesia. Although the laryngeal mask airway (LMA) does not provide a watertight seal, it has been used safely for positive pressure ventilation in both children and adults. Airway management is adequate in approximately 90% of infants and children.[1–5] The incidence of coughing, with and without desaturation, wheezing and hoarseness was significantly lower in the postoperative period using the LMA compared with the TT.[6] The use of closed circle systems has considerable advantages over semi-closed or semi-open systems in economy, limited atmospheric pollution, and maintenance of humidification and temperature.[7 8] These latter advantages are especially important in paediatric anaesthesia.

To assess the effectiveness of the LMA or uncuffed TT in anaesthesia techniques with reduced fresh gas flow rate, it is necessary to measure gas loss during positive pressure ventilation (PPV). Data derived from adults may not be applicable to children, as paediatric adaptations of both the LMA and TT differ considerably from the adult design.

We have investigated the efficacy of both airway devices with respect to respiratory variables, capnography and gas loss from a closed system during PPV, in a prospective, randomized study.

Patients and methods

With the approval of our institutional review board and written informed consent from parents, we studied 30 healthy children undergoing short elective surgical or diagnostic procedures with a predicted laryngeal mask airway size 2 (table 1). The study was prospective and randomized for insertion of a tracheal tube (TT) or a laryngeal mask airway (LMA). Randomization was performed using a random number generator. Even or odd numbers were assigned to either of the airway devices. Twenty of 30 children received laser treatment for facial portwine stains and 10 underwent diagnostic procedures of the eyes.

ANAESTHESIA

The children were allowed solids until 8 h and clear fluids until 3 h before anaesthesia. Midazolam 500 µg kg^{-1} was administered orally as premedication, 60 min before induction of anaesthesia. Anaesthesia was induced with propofol 2–3 mg kg^{-1} until disappearance of the eyelash reflex, followed by atracurium 0.4 mg kg^{-1} for neuromuscular block.[9] After ventilation of the lungs by mask with pure oxygen for 3 min, a TT or LMA was inserted. A size 2 LMA was used, as recommended by the manufacturers for children weighing 6.5–25 kg. The cuff of the LMA was inflated stepwise until the audible leak decreased. Cuff pressure was monitored continuously. To provide standardization a formula was used to calculate the size of the uncuffed TT

DIETER FRÖHLICH, MD, BARBARA SCHWALL, MD, WOLFGANG FUNK, MD, JONNY HOBBHAHN, MD, Department of Anaesthesia, University of Regensburg, 93042 Regensburg, Germany.
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Correspondence to D. F.

age-dependently, although a clinically based approach might result in a better fit of the tracheal tubes. The formula was as follows: internal diameter (id) = (16 + age (yr)) / 4 (mm). The wall thickness of the TT ranged from 0.76 to 0.91 mm.

After satisfactory ventilation with several manual breaths, the airway device was connected to the anaesthesia machine. Ventilation was continued as PPV. Tidal volume was set at 10 ml kg^{-1} and ventilatory frequency was adjusted based on end-tidal carbon dioxide readings. Anaesthesia was maintained with propofol 10 mg kg^{-1} h^{-1} and oxygen–air with an $F\text{I}_{\text{O}_2}$ of 0.4 until the end of the diagnostic or therapeutic procedure. All children were supine and were monitored during anaesthesia with non-invasive arterial pressure, ECG, pulse oximeter and an end-tidal gas monitor integrated into the anaesthesia ventilator. At the end of the surgical or diagnostic procedure, ventilation was switched from mandatory to assisted ventilation until spontaneous breathing recurred. Neuromuscular block was not antagonized. End-tidal carbon dioxide values were maintained at less than 5.3 kPa. The airway devices were left in place until patients opened their eyes.

ANAESTHESIA EQUIPMENT

The anaesthesia machine was a valveless high flow (70 litre min^{-1}) closed system device (PhysioFlex, Physio, Haarlem, The Netherlands). The core of this ventilator consists of up to four membrane chambers coupled in parallel (fig. 1).

When the patient is connected to the anaesthesia machine and it is switched to mechanical PPV, the inspiratory valve (valve 1 in fig. 1) opens and pressurized driving air enters the external part of the membrane chambers. After the preset tidal volume is reached, the inspiratory valve (1 in fig. 1) is closed and plateau pressure remains constant until expiration is started. Then the expiratory valve (3 in fig. 1) of the external part of the system is opened and pressure in the system returns to environmental pressure. The membranes move back towards the original position. The membranes are equipped with sensors so that total volume displacement of the system during ventilation can be measured. $F\text{I}_{\text{O}_2}$ and the volume inside the closed system are regulated by a computer using PID (proportional integrating and differentiating) regulating algorithms. Regulation of $F\text{I}_{\text{O}_2}$ is based on oxygen loss of the closed system and has the highest priority. The volume is regulated depending on the membrane position before and after each ventilation cycle. The computer maintains $F\text{I}_{\text{O}_2}$ and volume constant with 5-ml pulses of oxygen, or of the selected carrier gas (air or nitrous oxide), respectively. Leakage of the system corresponds to the carrier gas flow necessary to maintain the volume constant in the system. In the case of the system being completely airtight, there would be no carrier gas flow, as volume loss, oxygen uptake of the patient, is balanced by oxygen flow to the system and no additional carrier gas has to be added. This assumption that carrier gas flow equals leakage has limitations. First, it applies only to air as the carrier gas, as uptake of nitrous oxide or halogenated volatile anaesthetics by the patient would lead to volume loss and therefore to overestimation of leakage. Second, the fact that the lost gas contains oxygen and not only nitrogen leads to systematic

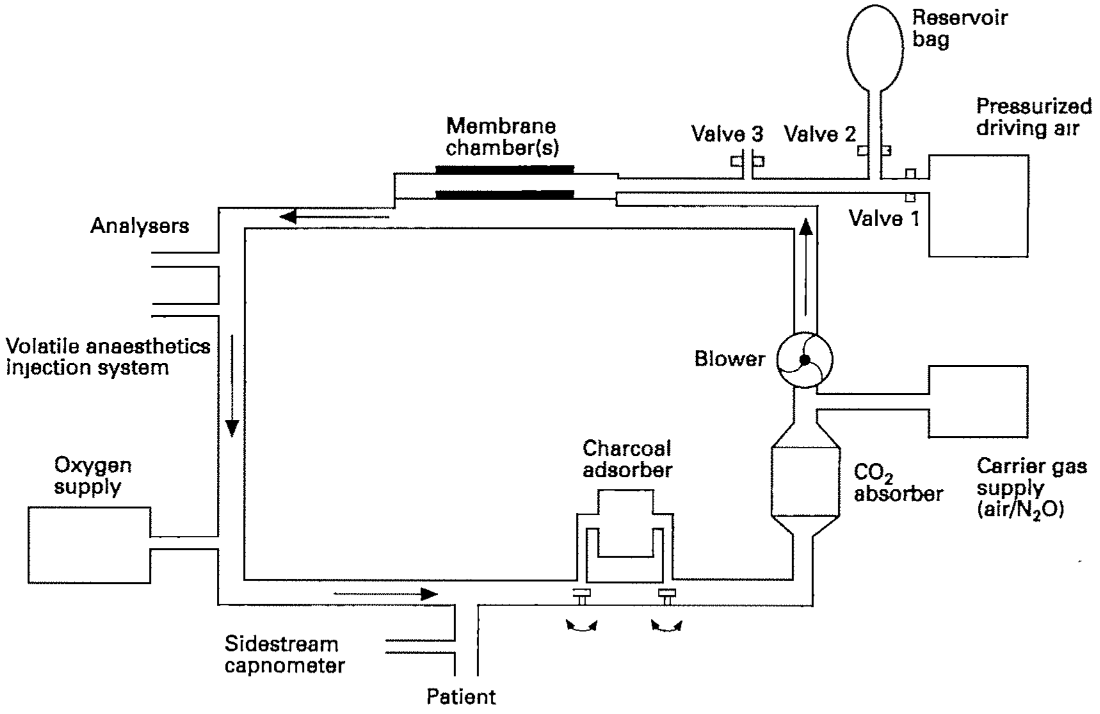

Figure 1 Schematic diagram of the valveless high flow (70 litre min^{-1}) closed system device (PhysioFlex) used in this study to assess leakage of the TT or LMA. The membranes of the chambers form an airtight barrier between driving pressurized air and the closed system. Valves are numbered 1–3: inspiratory valve or driving air inlet (1), valve to the reservoir bag (2) and expiratory valve or driving air outlet (3).

underestimation of the leakage of approximately 20%. This underestimation has been corrected in the values given in the summary.

The data presented are the mean values over 10 consecutive minutes after the anaesthesia device reached its steady state. This was assumed when the preset oxygen concentration of 35% was maintained stable for 5 min. Steady state was reached at 10–12 min after induction. Maximum errors for the oxygen and carrier gas feedback controls are 5%. The accuracy of the system for tidal volume is ±5% or 5 ml, for respiratory pressures ±10% or 0.27 kPa, and for gas flow rates ±5% or 10 ml min^{-1}, according to the manufacturer's data.

STATISTICAL ANALYSIS

All data, with the exception of data on gas flow rates, are presented as mean (SD). Taking account of the skewness of distributions, gas flow rates are given as median (range). To evaluate differences between groups the Student's *t* test was used for continuous variables with a normal distribution, whereas for continuous variables without a normal distribution the Mann–Whitney *U* test was used. Normality of distribution was tested by the Lilliefors test.[10] Fisher's exact test was used to compare nominal data differences. A significance level of $P \leq 0.05$ was considered significant. The sample size was calculated to have a power of 90% to detect a 10% difference in carrier gas flow.

Results

The two groups did not differ appreciably in age, weight and sex distribution (table 1). Ventilation was adequate in all cases; vital signs were within normal ranges during and after anaesthesia. Ventilatory frequencies, tidal volumes, peak pressures, plateau pressures and mean pressures were comparable in both groups (table 2).

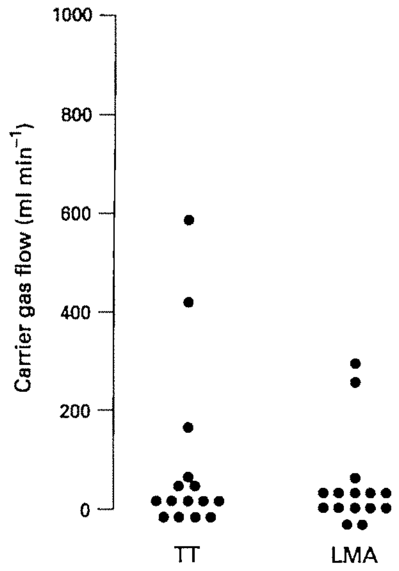

Figure 2 Carrier gas flow rates necessary to maintain the volume of the closed system stable during positive pressure ventilation in the TT and LMA groups. Carrier gas flow rate is fresh gas flow rate minus oxygen flow rate.

During emergence, we found no differences in complications such as laryngospasm, bronchospasm or hypersalivation. The incidence of coughing and breath-holding was higher in the TT group. The incidence of coughing was 53% (eight patients) with the TT and 13% (two patients) with the LMA ($P=0.05$). Breath-holding occurred in eight children (53%) in the TT group and in one child (7%) in the LMA group ($P=0.014$).

Fresh gas flow rate, oxygen uptake and air expenditure necessary to maintain the volume of the closed system stable are presented in figure 2 and table 3. Carrier gas flow was less than 100 ml min^{-1} in 13 (87%) patients in the LMA group and in 12 (80%) patients in the TT group.

End-tidal carbon dioxide was measured at the end of the respective device. In both groups a capnogram

Table 1 Patient characteristics in the TT and LMA groups (mean (SD) [min–max])

	TT ($n=15$)	LMA ($n=15$)
Age (months)	46 (10) [26–62]	41 (14) [24–71]
Sex (M/F)	11/4	9/6
Weight (kg)	16 (3) [11–20]	15 (3) [10–20]

Table 3 Gas flow rates om the TT and LMA groups (median (min–max))

	TT ($n=15$)	LMA ($n=15$)
Fresh gas flow (ml min^{-1})	123 (75–813)	86 (66–465)
Oxygen flow (ml min^{-1})	111 (75–229)	86 (65–172)
Carrier gas flow (ml min^{-1})	8 (0–584)	6 (0–293)

Table 2 Respiratory data in the TT and LMA groups (mean (SD) [min–max]) and the incidence of coughing and breath-holding during emergence. *$P \leq 0.05$, **$P \leq 0.014$

	TT ($n=15$)	LMA ($n=15$)
Ventilatory frequency (litre min^{-1})	16 (1) [14–18]	17 (2) [14–22]
Tidal volume (ml kg^{-1})	9.8 (1.1) [7.8–11.5]	10.6 (1.4) [8.5–14 1]
Total ventilation (litre min^{-1})	2.5 (0.5) [2.0–3.0]	2.6 (0.5) [2.0–3.0]
Peak pressure (kPa)	1.74 (0.19) [1.56–2.25]	1.72 (0.20) [1.27–1.96]
Plateau pressure (kPa)	1.30 (0.19) [1.45–3.08]	1 41 (0.19) [1 18–1 76]
Mean pressure (kPa)	0.55 (0.06) [0.49–0.68]	0.62 (0.11) [0.39–0.78]
PEEP (kPa)	0.19 (0.06) [0.1–0 20]	0.23 (0.08) [0.1–0.39]
Stat. lung compliance (ml kPa^{-1})	144 (43) [79–230]	135 (45) [80–245]
End-tidal CO_2 (kPa)	4.05 (0.48) [3.39–4.4]	4 23 (0.48) [3 47–4.72]
Breath-holding (%)	8 of 15 (53)	1 of 15 (7)**
(95% confidence interval)	(28–79)	(0–13)
Coughing (%)	8 of 15 (53)	2 of 15 (13)*
(95% confidence interval)	(28–79)	(5–22)

was recorded. Curves and data for end-tidal carbon dioxide were comparable in both groups.

Discussion

The desired tidal volume was delivered effectively in both groups. This is in accordance with studies in adults comparing an LMA with a cuffed TT.[11] We found no significant differences between the uncuffed TT and LMA with respect to the amount of oxygen or air necessary to maintain the volume of the closed system constant. Carrier gas flow was less than 100 ml min^{-1} in 13 (87%) patients in the LMA group and in 12 (80%) patients in the TT group (fig. 2). The maximum values of carrier gas loss were 584 ml min^{-1} (TT group) and 293 ml min^{-1} (LMA group). This low leakage in both groups would allow low flow or closed system anaesthesia to be undertaken appropriately. Devitt and co-workers investigated leakage of the LMA in adult patients during IPPV.[11] Leakage was assessed as the difference between expiratory and inspiratory volume. The leak increased depending on the applied airway pressure and they concluded that ventilation, using the LMA, is adequate if airway resistance and pulmonary compliance are normal. Gursoy, Algren and Skjonsby[12] investigated the amount of air leakage around LMA size 2 during IPPV with regard to gastric distension. The authors measured the circumference of the upper abdomen and found no significant difference between the TT and LMA. Neuromuscular blocking agents were used by these authors[12] only in the TT group and this may have influenced the comparison.

We observed a normal capnogram in both groups and mean end-tidal carbon dioxide was similar in both groups. Thus capnometry and capnography provide the necessary information for the anaesthetist on ventilatory status, correct placement of the airway device and accidental disconnection.

Chhibber and colleagues[13 14] studied Pa_{CO_2} and end-tidal carbon dioxide during IPPV via a TT or LMA in paediatric patients aged 1 month to 16 yr. They found that capnometric data were accurate and comparable with those recorded via a TT.

In accordance with the findings of Ferrari and Goudsouzian,[6] we found that the incidence of coughing and breath-holding was significantly lower in the LMA group. Nevertheless, the number of children studied was small and we cannot draw any conclusions on complications such as bronchospasm or laryngospasm. However, our findings demonstrate some of the advantages of the LMA in comparison with tracheal intubation. On the other hand, laryngeal masks do not always position well, particularly in small infants requiring a size 1 LMA.[2 5] Although the youngest children in this study were 2 yr of age, mean age was 3–4 yr. Therefore, the findings of this study may not reflect the situation in small infants.

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British Journal of Anaesthesia 1997; 79: 293–296

Caudal tramadol for postoperative analgesia in paediatric hypospadias surgery

D. P. PROSSER, A. DAVIS, P. D. BOOKER AND A. MURRAY

Summary

Ninety boys, aged 13–53 months, undergoing repair of hypospadias, were allocated randomly to receive 0.8 ml kg^{-1} of one of three solutions into the caudal extradural space: group B received bupivacaine 2 mg kg^{-1}, group T received tramadol 2 mg kg^{-1} in 0.9% saline and group BT a mixture of both. Postoperative pain was assessed hourly for 12 h after injection using a modified TPPPS pain score and additional analgesia was administered to those children whose pain scores were >3/10. Nine patients (30%) in group T required additional analgesia within 1 h of surgery compared with only two (6.7%) and three (10%) patients in groups B and BT, respectively (P=0.04). Mean duration before additional analgesia was required in the remaining patients was 9.3 (SD 3.0) h in group B, 10.7 (2.2) h in group T and 10.5 (2.0) h in group BT (P>0.20). There were no significant differences between the groups in mean ventilatory frequency, sedation scores, incidence of emesis, facial flushing or pruritus. We conclude that caudal tramadol had a slow onset of action and that the addition of tramadol to bupivacaine, when both drugs were administered caudally, did not significantly prolong the duration of action of bupivacaine. (*Br. J. Anaesth.* 1997; **79**: 293–296).

Key words

Analgesia, paediatric. Analgesic techniques, extradural. Anaesthetics local, bupivacaine. Analgesics opioid, tramadol. Surgery, urological. Pain, postoperative.

Although administration of bupivacaine into the caudal extradural space has been our standard method of providing postoperative analgesia for hypospadias repair, a single injection may have only a relatively short duration of action.[1–4] Placement of a catheter into the extradural space either at the caudal or lumbar region adds to the risk of infection and tends to prevent early mobilization.[5] Attempts to overcome these problems by combining local anaesthetic agents with other drugs such as adrenaline,[1,2] clonidine,[2] ketamine[2,3] or various opioids[4,6–10] have met with varied degrees of success. Problems with emesis, sedation, nausea, itching or respiratory depression have limited their usefulness.[11]

Tramadol, a synthetic 4-phenyl-piperidine analogue of codeine, has been available in the UK since 1994, although is it licensed only for use in children aged >12 yr. Tramadol is a racemic mixture of two enantiomers, (+)-tramadol and (−)-tramadol. The (+)-enantiomer has a moderate affinity for the opioid μ receptor, greater than that of the (−)-enantiomer.[12] In addition, the (+)-enantiomer inhibits serotonin uptake and the (−)-enantiomer is a potent noradrenaline inhibitor, complementary properties which result in a synergistic antinociceptive interaction between the two enantiomers.[12] The result is an opioid with a striking lack of respiratory depressant effect despite an analgesic potency approximately equal to that of pethidine.[13–15] Furthermore, animal work has suggested that tramadol may have a selective spinal action.[16,17] Tramadol has been shown to provide effective, long lasting analgesia after extradural administration in both adults[18,19] and children[20] and prolongs the duration of action of mepivacaine used for brachial plexus block.[21]

We wished to determine if caudal tramadol could provide effective, long lasting analgesia and if the addition of tramadol to bupivacaine would significantly extend the duration of analgesia produced by bupivacaine alone.

Patients and methods

After obtaining local Ethics Committee approval and written, informed parental consent, we studied 90 healthy boys, ASA I–II, aged 13–53 months, who required surgical repair of hypospadias. Those children receiving medication likely to have interactions with opioids or cause sedation, those in whom caudal analgesia was contraindicated and those being discharged on the day of surgery were excluded.

No premedication was used. After cannulation of a vein, anaesthesia was induced with thiopentone 5 mg kg^{-1} and tracheal intubation was facilitated

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D. P. PROSSER*, FRCA, A. DAVIS, FRCA, P.D. BOOKER, FRCA, A MURRAY, FRCA, Department of Anaesthesia, Royal Liverpool Children's NHS Trust, Eaton Road, Liverpool L12 2AP.

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*Present address: Department of Anaesthesia, University Hospital of Wales, Heath Park, Cardiff CF4 4XW

Correspondence to P. D. B.

Table 1 Modified TPPPS pain score. The same variables validated in the original score were used, but scored so that the maximum score was 10, rather than 7 as in the original. The five pain behaviour items were scored hourly during a 5-min observation period. Each variable was defined as in the original TPPPS score[22]

Variable	Score 0	Score 1	Score 2
Verbal complaint/cry	None	Once only	>Once
Groan/moan/grunt	None	Once only	>Once
Facial expression	Neutral	One grimace	Grimace>once
Restless motor behaviour	None	One episode only	>One episode
Rub/touch painful area	None	Once only	>Once

using atracurium 0.5 mg kg^{-1}. Anaesthesia was maintained with 1–1.5% isoflurane and 70% nitrous oxide in oxygen. Patients were allocated randomly (sealed envelope, random number table) to receive one of three solutions, diluted with 0.9% saline as necessary, so that the volume injected into the caudal extradural space was 0.8 ml kg^{-1}. Group B received bupivacaine 2 mg kg^{-1}, group T tramadol 2 mg kg^{-1} and group BT bupivacaine 2 mg kg^{-1} together with tramadol 2 mg kg^{-1}. No other peroperative analgesia was given. Anaesthesia was discontinued when the wound dressing had been applied; residual neuromuscular block was antagonized with neostigmine 50 μg kg^{-1}, given together with atropine 20 μg kg^{-1}, and the patient's trachea was extubated before transfer to the recovery area.

When the patient was awake in the recovery area, heart rate, arterial pressure, peripheral oxygen saturation, ventilatory frequency and pain score were recorded before discharge to the surgical ward. On arrival in the surgical ward a research nurse, who was unaware of the nature of the caudal injection, performed hourly observations until 12 h after the caudal injection. A TPPPS pain score,[22] modified to give a maximum score of 10 (table 1), was used to assess pain over a 5-min period every hour. Ventilatory frequency and a four-point sedation score (0=eyes open spontaneously; 1=eyes open to speech; 2=eyes open when shaken; 3=unrousable)[23] were also measured hourly. A pain score >3/10 resulted in administration of either i.v. morphine 100 μg kg^{-1} or oral paracetamol 20 mg kg^{-1}, as deemed appropriate. Episodes of nausea, vomiting, facial flushing or pruritus were noted if they occurred.

Mean age, weight, pain and sedation scores, and time to additional analgesia in each group were compared with each other using one-way analysis of variance (ANOVA) with *post hoc* comparisons using the Bonferroni multiple range test. The Pearson chi-square test with Fisher's exact test were used to compare the incidence of use of postoperative urinary catheters and complication rates in the three groups.

Results

Median age and weight of the patients were similar in all three groups (table 2). There were significantly more patients requiring additional analgesia in the recovery room immediately after surgery in group T compared with the two other groups (P=0.04) (table 2). Mean hourly pain scores in the three groups who left the recovery room without first requiring additional analgesia were similar from 4 h after injection and thereafter. However, the mean score in group T was significantly higher than that in groups B and BT 3 h after injection (fig. 1).

Mean duration of analgesia for those patients who left the recovery area without first requiring additional analgesia did not differ significantly between groups (table 3).

There were no significant differences between the three groups in mean hourly sedation scores or ventilatory frequencies. Although the incidence of

Table 2 Median (range) age and weight, and number of patients requiring morphine in the recovery room (RR) in the three groups of patients. Group B received bupivacaine 2 mg kg^{-1}, group T tramadol 2 mg kg^{-1} and group BT bupivacaine 2 mg kg^{-1} together with tramadol 2 mg kg^{-1}. All drugs were injected into the caudal extradural space and diluted in 0.9% saline as necessary to a total volume of 0.8 ml kg^{-1}

	Group B (n=30)	Group T (n=30)	Group BT (n=30)	P
Age (months)	25 (15–52)	26 (13–39)	21 (14–53)	0.54
Weight (kg)	12 3 (9.2–17.3)	12 9 (8.9–16.6)	12.3 (9.9–20.0)	0.71
No. of patients requiring analgesia in RR (%)	2 (6.7)	9 (30.0)	3 (10.0)	0.04
No. of patients requiring urinary catheter (%)	12 (40 0)	11 (36.7)	11 (36.7)	0.61

Table 3 Mean (SD) sedation score, hourly ventilatory frequency and duration of analgesia in the three groups of patients. Group B received bupivacaine 2 mg kg^{-1}, group T tramadol 2 mg kg^{-1} and group BT bupivacaine 2 mg kg^{-1} together with tramadol 2 mg kg^{-1} All drugs were injected into the caudal extradural space and diluted in 0.9% saline as necessary to a total volume of 0.8 ml kg^{-1}

	Group B	Group T	Group BT	P
Sedation score	0.66 (0.33)	0.66 (0.30)	0.68 (0.27)	0.97
Ventilatory frequency	26.9 (4.2)	29.3 (8.8)	27.6 (5.7)	0.45
Duration of analgesia (h)	9.3 (3.0)	10.7 (2.2)	10.5 (2.0)	0.72

Table 4 Incidence of postoperative complications in the three groups of patients. Group B received bupivacaine 2 mg kg^{-1}, group T tramadol 2 mg kg^{-1} and group BT bupivacaine 2 mg kg^{-1} together with tramadol 2 mg kg^{-1}. All drugs were injected into the caudal extradural space and diluted in 0.9% saline as necessary to a total volume of 0.8 ml kg^{-1}. Data on complications occurring only in the recovery room and on patients requiring morphine in the recovery room have been excluded

	Group B (*n*=28)	Group T (*n*=21)	Group BT (*n*=27)	*P*
No. of patients c/o emesis (%)	3 (10.7)	6 (28.6)	5 (18.5)	0.27
No. of patients c/o pruritus (%)	1 (3.6)	1 (4.8)	1 (3.7)	1.00
No. of patients c/o flushing (%)	9 (32.1)	7 (33.3)	9 (33.3)	1.00
No. of patients c/o numbness (%)	1 (3.6)	0 (0.0)	1 (3.7)	1.00

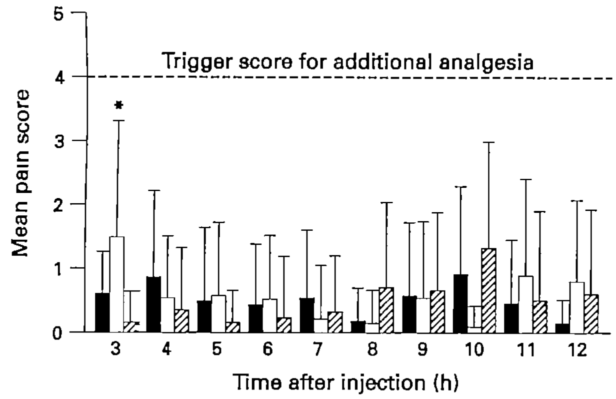

Figure 1 Mean hourly pain scores in the three groups of patients from 3 to 12 h after caudal injection. Group B (■) received bupivacaine 2 mg kg^{-1}, group T (□) tramadol 2 mg kg^{-1} and group BT (▨) bupivacaine 2 mg kg^{-1} together with tramadol 2 mg kg^{-1}. All drugs were injected into the caudal extradural space and diluted in 0.9% saline as necessary to a total volume of 0.8 ml kg^{-1}. Data for patients requiring morphine in the recovery room have been excluded *$P<0.05$.

emesis was higher in both tramadol groups (T and BT) than in the bupivacaine group, the differences were not statistically significant (table 4). The incidence of pruritus and numbness was low in all groups. Surprisingly, the incidence of noticeable facial or more generalized flushing, or both, exceeded 30% in all three groups, although it was not obviously distressing to the individuals affected.

Discussion

We have found that tramadol, when injected into the caudal extradural space, produced useful analgesia for up to 12 h after hypospadias surgery. However, if the period of time between performing the caudal injection and recovery of the child from anaesthesia was <2 h, the incidence of immediate pain (requiring rescue analgesia) was high (30%), demonstrating a slow onset of action of caudal tramadol. However, if the operation was longer, then caudal tramadol produced good quality analgesia for an average of 10.7 (2.2) h. Although adding tramadol to our usual dose of caudal bupivacaine slightly prolonged the mean duration of action of bupivacaine, the difference was not statistically significant.

Studies in rodents[16 17] suggested that tramadol has a selective spinal action similar to that of other opioids. This view was supported indirectly by one clinical study in adults which found much lower serum concentrations of tramadol after extradural injection[24] than were described subsequently after i.v. injection.[25] It is not clear if the delay in onset of tramadol analgesia observed in our study was caused by slow absorption across the dura or slow uptake of tramadol from the extradural space into the systemic circulation. Tramadol has a lipid solubility comparable with that of morphine, which may account for its slow onset of action. However, most clinical studies that have examined the effects of extradural tramadol[18–20 26] have used dose regimens that are broadly similar to those used i.v.[13–15 27–30] Furthermore, preliminary results from our on-going pharmacokinetic study, which have shown that mean serum concentrations 2–8 h after either i.v. or caudal injections of tramadol are not significantly different, tend to support the view that systemic absorption of extradural tramadol may be necessary for its action.

Although a previous study demonstrated that tramadol, when added to mepivacaine, significantly prolonged the duration of brachial plexus block,[21] we could not demonstrate that the addition of tramadol prolonged significantly the action of caudal bupivacaine. However, the mean duration of action of caudal bupivacaine in our study appeared somewhat longer than that found in previous studies.[2 9 31 32] Differences in the operations performed, method of pain scoring, bupivacaine dose and volume, and calculation of analgesia time probably account for this discrepancy.

Eleven or 12 children in each group (37–40%) required an indwelling urinary catheter for some days after surgery; there was no significant difference in this incidence between groups ($P=0.61$) (table 2). Often the first indication for additional analgesia in these children was related to acute attacks of "bladder spasm". These short-lasting periods of intense discomfort seem peculiar to children requiring an indwelling urinary catheter after hypospadias surgery, for surgical reasons, and it is possible that the duration of tramadol analgesia may be longer in patients not subject to such problems. The duration of analgesic action was taken as the time from caudal injection to first administration of supplementary analgesia. If by 12 h no additional analgesia had been required, we assumed for the sake of comparison that the duration of analgesia was 12 h, although it is possible that useful analgesia may have continued for longer. However, logistical problems dictated that further observations were impracticable and after the 12 h observations were complete, there was a tendency for prophylactic paracetamol analgesia to be given by the ward nurses to any patient who was still awake. All patients were managed successfully with paracetamol alone after this time.

In conclusion, we have shown that when a single caudal injection of tramadol was used in young children it provided analgesia for up to 12 h without a significant incidence of side effects. However, the slow onset time of caudal tramadol necessitated that it was given with a local anaesthetic agent such as bupivacaine to ensure good analgesia on recovery from anaesthesia. As an adjunct to bupivacaine, tramadol may prove more useful in young children and infants than other opioids because of its lack of respiratory depressant effects. However, this property may imply that there is little advantage in injecting tramadol into the extradural space and that i.v. administration may be equally efficacious. Further dose-ranging and pharmacokinetic studies in young children are required before the optimum route of administration of tramadol can be determined.

Acknowledgements

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Comparison of single, end-holed and multi-orifice extradural catheters when used for continuous infusion of local anaesthetic during labour

M. A. S. DICKSON, C. MOORES AND J. H. MCCLURE

Summary

Single, end-holed and multi-orifice extradural catheters were compared in terms of efficacy and complications when used for infusion of 0.1% bupivacaine during labour. In this study of 364 patients there was no difference in unilateral block after an initial bolus dose (18 (11.5%) for single, end-holed and 16 (10.9%) for multi-orifice catheters). Unilateral block recurred with seven (4.0%) single, end-holed and with eight (4.8%) multi-orifice catheters. Unilateral blocks, arising for the first time during infusion of local anaesthetic, occurred significantly more frequently when single, end-holed catheters were used (29 (16.4%)) compared with multi-orifice catheters (14 (8.4%)) ($P<0.05$). (*Br. J. Anaesth.* 1997; **79**: 297–300).

Key words
Equipment, catheters extradural. Anaesthesia, obstetric.

There are two types of extradural catheter currently available in the UK: the single or end-holed and the multi-orifice (lateral eyed) catheter. Comparisons have been made in relation to complications associated with their use.[1–3] Single, end-holed catheters avoid the risk of partial subarachnoid or vascular placement, a recognized problem with multi-orifice catheters.[4] Multi-orifice catheters, however, are considered to allow more even spread of local anaesthetic within the extradural space.[2 3] All studies to date have considered only the quality of analgesia and complications after bolus injection of local anaesthetic. This study was undertaken to compare the efficacy and incidence of complications during continuous extradural infusion of local anaesthetic.

Patients and methods

The study was approved by the local Ethics Committee and took place over a 2-yr period. Verbal informed consent was obtained from all participants. As we were studying two types of catheter in routine use in the unit, and as the observations being made were standard practice, the Ethics Committee considered that written consent was not required. Mothers who requested extradural analgesia for labour pain were included in the study if they were in early labour or not expected to deliver within 3 h. Consultant and trainee anaesthetists working in the Simpson Memorial Maternity Pavilion, Royal Infirmary of Edinburgh, participated by including suitable patients, using a standard extradural technique and recording data during extradural infusion.

Patients were allocated randomly using computer generated random numbers and a sealed envelope technique to receive either a single, end-holed or a multi-orifice catheter. Using a 16-gauge Portex disposable Tuohy needle, the extradural space was identified by loss of resistance to saline. A volume not exceeding 4 ml of normal saline was injected into the extradural space. The catheter was passed in a cranial direction leaving 2–4 cm of single, end-holed or 3–5 cm of multi-orifice catheter within the extradural space. These lengths were chosen on the basis of current practice within the unit. It was intended that the proximal orifices of the multi-orifice catheters would lie in a similar position within the extradural space as the orifice of the single, end-holed catheters. After negative aspiration of the catheter a test dose of 2% lignocaine 4 ml was given. A record was made of dural puncture, cerebrospinal fluid aspiration from the catheter, paraesthesia on catheter insertion, whether or not the meniscus within the catheter decreased easily, blood in the catheter or symptoms of systemic toxicity after the test dose. The extradural block was established with 0.25% or 0.5% bupivacaine 8 ml, as considered necessary on clinical grounds by the anaesthetist at that time. After 20 min, block height was assessed on both sides of the abdomen or upper legs using ethyl chloride spray and the quality of analgesia was recorded as good, moderate or poor. A standard continuous infusion of 0.1% bupivacaine was commenced at 20 ml h^{-1}. Additional top-up doses of 0.25% bupivacaine 8 ml were prescribed, to be given by the attending midwife. Occurrence of unilateral block, missed segment and quality of analgesia were assessed by the midwife using a three-point pain score. The anaesthetist was called on the first occasion that a unilateral block was demonstrated

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M. A. S. DICKSON, FFARCSI, C. MOORES, FRCA, J. H. MCCLURE, BSC (HONS), FRCA, Department of Anaesthetics, Royal Infirmary of Edinburgh, Lauriston Place, Edinburgh. Accepted for publication: March 28, 1997.

Table 1 Features of insertion of the two extradural catheters. $^{**}P<0.01$

Catheter type	Dural puncture	CSF on aspiration	Paraesthesia on insertion	Meniscus decreases easily	Blood in catheter	Toxic symptoms on test dose
Single, end-holed	1 (0.5%)	0	44 (23.0%)	140 (88.6%)	8 (4.3%)**	3 (1.6%)
Multiorifice	1 (0.5%)	0	34 (19.4%)	149 (85.6%)	21 (12.1%)**	3 (1.7%)
No record	2	0	0	17	8	0

and the extent of block was assessed by ethyl chloride spray. Any treatment required was recorded and the block was reassessed by the anaesthetist 20 min later.

Data were analysed statistically using the chi-square method with Yates' correction. $P<0.05$ was considered significant.

Results

We collected and analysed 364 records. There were two dural punctures with the Tuohy needle but no catheter was identified as being within the subarachnoid space. Transient paraesthesia on insertion of the catheter was experienced by 44 patients in the single, end-holed group and by 34 patients in the multi-orifice group (table 1). Bupivacaine 0.25% was used to produce block in 54.1% of participants in the multi-orifice group and in 51.4% of participants in the single, end-holed group. Bupivacaine 0.5% was used to produce block in 45.9% of participants in the multi-orifice group and in 48.6% of participants in the single, end-holed group (ns; chi-square test). The meniscus of fluid within the catheter was seen to decrease easily when the catheter was raised above the point of insertion in similar numbers in each group (140 *vs* 149) (table 1). Six patients experienced symptoms of systemic toxicity after the test dose of local anaesthetic. In two cases the catheter was resited (both single, end-holed catheters) and one multi-orifice catheter was withdrawn by 1 cm. In the three other cases there was no record of the action taken. The multi-orifice catheter group had an increased incidence of blood tinged fluid in the catheter on insertion (21 *vs* 8) ($P<0.01$) (table 1).

Quality of analgesia was recorded as good with no evidence of unilateral block or missed segments in 140 (86%) patients in the single, end-holed group and in 132 (86%) patients in the multi-orifice group (table 2).

Table 2 Adequacy of analgesia after initial establishment of block

	Analgesia after block produced		
Catheter type	Good	Moderate	Poor
Single, end-holed	140	18	5
Multi-orifice	132	17	4

There was no significant difference between the two groups (18 *vs* 16) in the incidence of unilateral block at the 20-min assessment (table 3). After satisfactory bilateral block had developed with an additional local anaesthetic bolus, a similar number of patients (seven of 18 in the single, end-holed group and eight of 16 in the multi-orifice group) subsequently developed recurrence of the unilateral block (ns) (table 3). The incidence of a new unilateral block developing during infusion of the local anaesthetic was 29 (16.4%) in the single, end-holed group and 14 (8.4%) in the multi-orifice group ($P<0.05$) (table 3).

Intervention required for treatment of unilateral block was minimal in that only two catheters were resited. Withdrawal of the catheter, top-up of local anaesthetic or local anaesthetic with fentanyl, posture or a combination of these sufficed for all others.

Discussion

Continuous infusion of dilute local anaesthetic solution into the extradural space is now a commonly used technique for analgesia in labour.[5] There has been a need for clinical investigation into the performance characteristics of the two extradural catheter types when used for a continuous infusion technique. Previous studies comparing the two catheter types after bolus administration have produced different results.[1–3] In this study the distribution of sensory block obtained with the two types of catheter in common use was examined during infusion of dilute local anaesthetic.

Single, end-holed catheters have been advocated by some as being inherently safer as partial subarachnoid or vascular placement is avoided. In a radiological study, Beck and colleagues identified a frequency of 11.5% partial vascular and 0.9% partial subarachnoid placement of multi-orifice catheters and recommended that these catheters should not be used.[4] Ward and colleagues reported a death associated with the use of a double orifice catheter caused by partial subarachnoid placement.[6] Although this

Table 3 Occurrence of unilateral block on initially siting extradural block and development of unilateral block while extradural infusion was in progress. $^{*}P<0.05$

		Unilateral block developing during infusion	
Catheter type	Unilateral block on producing extradural	Recurrence of unilateral block	New unilateral block developing during infusion
Single, end-holed	18 (11.5%)	7 (4.0%)	29 (16.4%)*
Multiorifice	16 (10.9%)	8 (4.8%)	14 (8.4%)*

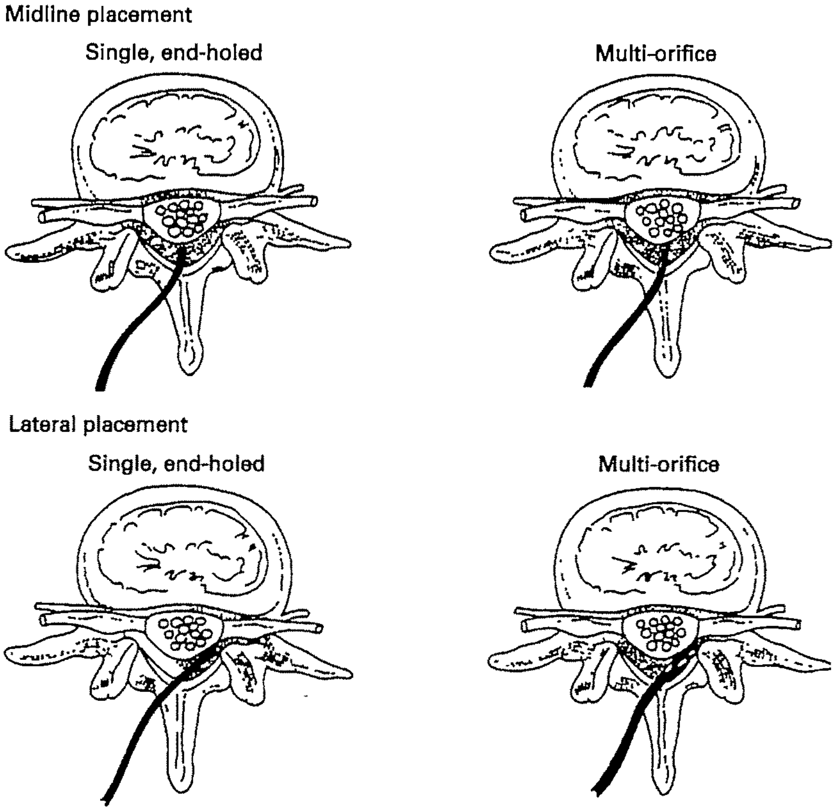

Figure 1 Spread of local anaesthetic in the extradural space administered by low pressure infusion through single, end-holed and multi-orifice catheters placed in the midline or laterally. Spread of local anaesthetic is shown as shading. Top: midline placement of either catheter type results in bilateral spread of local anaesthetic in the extradural space. Bottom: when placed laterally, unilateral block develops with single, end-holed catheters, but bilateral spread may occur with multi-orifice catheters as local anaesthetic preferentially emits from the proximal, centrally positioned orifice during low pressure infusion.

type of catheter is not identical to the multi-orifice catheter, the potential for such misplacement still exists. It has been demonstrated *in vitro* that when multi-orifice catheters are used for bolus administration, the distribution of local anaesthetic is dependent on the rate and pressure of the injection with most of the solution emitting from the proximal orifice when a low injection rate and pressure are used.[6,7] However, some of the potentially serious shortcomings of the multi-orifice catheter have been viewed by some workers as positive benefits.[8] With unidentified partial subarachnoid, intravascular placement or late catheter migration, the volume of local anaesthetic deposited outside the extradural space may be reduced. With end-holed catheters late catheter migration may result in a considerably larger volume of local anaesthetic entering the subarachnoid space.

In this study there was no accidental subarachnoid or intravascular catheter placement of local anaesthetic administration during the initial bolus dose or infusion in either group, but six patients had a reaction to the test dose. There was no difference between the two groups in the incidence of dural puncture using the Tuohy needle, the incidence of low resistance, as assessed by the meniscus decreasing easily, or paraesthesia, on catheter insertion.

Blood was found in the catheter significantly more frequently in the multi-orifice group. These findings are similar to those of previous studies.[1,2] This increased incidence in association with multi-orifice catheters is considered to be a result of a higher detection rate of vascular trauma rather than an increased incidence of vascular placement.[1] Collier and Gatt reported one case of intravascular placement with negative aspiration of blood from a single, end-holed catheter, perhaps because the end hole was against the vessel wall.[3] Satisfactory analgesia during labour requires bilateral spread of local anaesthetic within the extradural space. After bolus administration Michael, Richmond and Birks demonstrated that at 30 min there was more even distribution of local anaesthetic using multi-orifice catheters as evidenced by a significantly reduced incidence of unilateral block or missed segments compared with single, end-holed catheters.[2] Collier and Gatt found an unacceptably high incidence of unsatisfactory block with single, end-holed catheters (32% in the single, end-holed group compared with 12% in the lateral eye catheters).[3] In contrast, after a bolus dose of local anaesthetic, Morrison and Buchan were unable to detect any difference in incidence of unilateral block comparing the two catheter types at initial assessment.[1]

Interestingly, a recent study using a 10-ml bolus of radio-opaque contrast medium demonstrated more even distribution of dye within the extradural space with single, end-holed catheters compared with multi-orifice catheters.[9]

Our clinical study supports the findings of Morrison and Buchan[1] in that there was no difference in the incidence of unilateral block after bolus administration. Seven patients in the single, end-holed group and eight patients in the multi-orifice group had recurrence of unilateral block. During infusion of the local anaesthetic, 29 of 163 (16.4%) patients in the single, end-holed group and 14 of 153 (13%) patients in the multi-orifice group developed a new unilateral block. The higher incidence of unilateral blocks occurring for the first time in the single, end-holed catheter group during extradural local anaesthetic infusion was significant.

Midline placement of both types of catheter is presumed to result in bilateral spread of local anaesthetic (fig. 1, top). This would also be the case with lateral placement of a multi-orifice catheter inserted in the midline, as most of the volume of local anaesthetic infused at a low pressure takes the path of least resistance through the proximal orifice which is placed centrally. However, with lateral placement the end hole of a single, end-holed catheter deviates from the midline and distribution of an infusion of local anaesthetic is unilateral (fig. 1, bottom). It is our suggestion that this unilateral distribution may be overcome by bolus administration of a larger volume producing spread to the opposite side. As an initial bolus dose of local anaesthetic (0.25% or 0.5% bupivacaine 8 ml) was used to produce extradural block, lateral placement of a single, end-holed catheter may not be immediately apparent.

The length of catheter in the extradural space may influence spread of local anaesthetic. In this study, single, end-holed catheters were inserted for 2–4 cm into the space and multi-orifice catheters 3–5 cm, which reflected the current clinical practice in the maternity hospital. Michael, Richmond and Birks[2] placed 1.5 cm of single, end-holed and 2.5 cm of lateral eyed catheters into the extradural space. Collier and Gatt[3] placed 3–4 cm of either catheter type in the space and suggested that this may be too great for a single, end-holed catheter. Morrison and Buchan[1] inserted 3 cm or less of each catheter type in the space without observing any difference in the incidence of unilateral block. Beilin, Bernstein and Zucker-Pinchoff showed that 5 cm was optimal for a multi-orifice catheter.[10]

The advantage of more even spread of a local anaesthetic should be balanced against the danger of multi-compartment block. No multi-compartment blocks were detected in our study, or in other controlled studies comparing the two catheter types. A newer multi-orifice catheter with the holes distributed more closely together may reduce the risk of multi-compartment block while providing more even distribution of local anaesthetic during low pressure infusion.[11] On the basis of this study the choice of catheter may be more important if the anaesthetist chooses to use continuous infusion of weak solutions of local anaesthetic. A multi-orifice catheter would appear to reduce the risk of the patient developing unilateral extradural block and may be preferable when administering local anaesthetic by continuous infusion at a rate of $20\ \text{ml h}^{-1}$.

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Transient neurological symptoms after spinal anaesthesia with 4% mepivacaine and 0.5% bupivacaine

A. HILLER AND P. H. ROSENBERG

Summary

Several studies have reported transient neurological symptoms after spinal anaesthesia with 5% lignocaine. In order to evaluate the role of concentrated solutions of local anaesthetic in the development of transient neurological symptoms, 200 ASA I or II patients undergoing minor orthopaedic or rectal surgery under spinal anaesthesia were allocated randomly to receive 4% mepivacaine 80 mg or hyperbaric 0.5% bupivacaine 10 mg. All patients were interviewed by an anaesthetist approximately 24 h after spinal anaesthesia, and after 1 week patients were asked to return a written questionnaire. The incidence of transient neurological symptoms consisting of pain in the buttocks or pain radiating symmetrically to the lower extremities differed ($P<0.001$) between patients receiving mepivacaine (30%) and those receiving bupivacaine (3%). Hyperbaric 0.5% bupivacaine can be recommended for minor operations on the lower abdomen or lower extremities. (*Br. J. Anaesth.* 1997; **79**: 301–305).

Key words
Anaesthetic techniques, subarachnoid. Anaesthetics local, mepivacaine. Anaesthetics local, bupivacaine. Complications, neurological.

The first report of transient neurological symptoms, termed initially transient neurological impairment or transient radicular irritation, after spinal anaesthesia with hyperbaric 5% lignocaine by Schneider and colleagues in 1993[1] was confirmed later by several other studies.[2–6] It is thought that a localized local anaesthetic toxic effect may be an important contributing factor in the development of transient neurological symptoms after spinal anaesthesia with concentrated solutions.[7 8] The occurrence of this complication is rare after the use of 0.5% bupivacaine for spinal anaesthesia.[5 9 10]

Mepivacaine has been used for spinal anaesthesia since the beginning of the 1960s.[11] In the first large-scale report of 20 000 mepivacaine spinal anaesthetics, outcome was favourable and no neurological complications were noted.[12] However, as with 5% hyperbaric lignocaine, the hyperbaric spinal anaesthetic solution of mepivacaine is also quite concentrated (4%) and post-spinal sequelae similar to those after hyperbaric lignocaine spinal anaesthesia should be expected. In this study, we examined the occurrence of transient neurological symptoms after spinal anaesthesia with either 4% hyperbaric mepivacaine or hyperbaric 0.5% bupivacaine.

Patients and methods

Two hundred ASA I or II patients undergoing minor orthopaedic, varicose vein, rectal or gynaecological operations were studied in a randomized, double-blind manner (table 1). Patients with a pre-existing neurological disease or diabetes mellitus were excluded. The study was approved by the Ethics Committee of the hospital, and informed consent was obtained from the patients.

All patients were premedicated with diazepam 5–15 mg orally. Patients were allocated randomly by sealed envelope to receive 4% mepivacaine 80 mg with glucose 95 mg ml^{-1} (Scandicain 40 mg ml^{-1}, Astra, Wedel, Germany) or 0.5% hyperbaric bupivacaine 10 mg with glucose 80 mg ml^{-1} (Marcain spinal 5 mg ml^{-1}, Tung, Astra, Södertälje, Sweden). An identical volume of 2 ml was drawn into a syringe by an independent anaesthesia nurse so that the anaesthetist (A. H.) performing the block was unaware of which drug was given. Although the doses are not equipotent from a theoretical point of view, similar spread and duration of spinal anaesthesia have been observed after a dose of 10 mg of 0.5 % hyperbaric bupivacaine and 80 mg of hyperbaric mepivacaine.[13 14]

A peripheral i.v. infusion with acetated Ringer's solution was started before operation. Thereafter spinal anaesthesia was performed at the L3–4 interspace with the patient in the lateral position using a 27-gauge Quincke needle. However, if the puncture was considered difficult, a higher interspace, larger needle or the sitting position was chosen to perform spinal anaesthesia. Free flow of cerebrospinal fluid was verified before and after injection of the local anaesthetic. Immediately after spinal puncture, the patient was turned to the supine position with the operating table in a slight head-up tilt position.

A. HILLER, MD, PHD, Department of Anaesthesia, Kuusankoski District Hospital, FIN-45750 Sairaalamäki, Finland P. H. ROSENBERG, MD, PHD, Department of Anaesthesiology, Helsinki University Central Hospital, FIN-00290 Helsinki, Finland.
Accepted for publication: April 10, 1997.
Correspondence to A. H.

Patients were monitored with electrocardiography, automated arterial pressure and pulse oximetry. Hypotension (systolic arterial pressure <90 mm Hg or >30% decrease from baseline) was treated with 5-mg increments of ephedrine or 200-μg increments of phenylephrine. Bradycardia (heart rate <50 beat min^{-1}) was treated with atropine 0.5 mg or glycopyrronium 0.2 mg.

Testing of pinprick analgesia and motor block was performed at 5, 10, 15, 60 min, and thereafter at 30-min intervals. A modified Bromage scale was used for testing motor block: 0=no paralysis (full flexion of the knees and feet), 1=inability to flex the extended leg (just able to move the knees), 2=inability to flex the knee (able to move the feet only), 3=inability to flex the ankle joint (unable to move the feet or knees). Patients were discharged from the recovery room when recovery of motor block was complete. Nurses on the ward recorded the time when patients reported that they had normal sensation in the buttocks and feet.

All patients were interviewed by the investigator on the first postoperative morning. They were asked if they had experienced any of the symptoms on the following standardized symptom checklist: headache, backache, pain not associated with surgery, sensory disturbances, change in muscle strength, or difficulties in voiding or in hearing. Special attention was paid to lower extremity symptoms, type of pain and radiation of pain.[3]

One week after spinal anaesthesia, patients were asked to return a mailed questionnaire. They were asked to mention symptoms which they particularly associated with spinal anaesthesia. Enquiries concerning symptoms and their duration included headache, backache, pain in the operation area and pain in the thighs, buttocks, calves or elsewhere. Patients were also asked to assess the degree of satisfaction with their spinal anaesthesia.

Transient neurological symptoms were defined as symmetrical bilateral pain in the back or buttocks or pain radiating to the lower extremities after recovery from spinal anaesthesia.

Student's t test and Fisher's exact test were used to compare differences. $P<0.05$ was considered significant.

Results

The characteristics of the patients and details of the operations and spinal anaesthetic procedures are summarized in tables 1 and 2. Motor block was complete in 96% of patients in the mepivacaine group and in 81% of patients in the bupivacaine group ($P<0.001$). Details of motor block are presented in table 3. In one case, bupivacaine provided inadequate surgical anaesthesia although free flow of cerebrospinal fluid was verified before and after injection of the drug.

Eighty-nine of 99 (90%) patients in the mepivacaine group and 88 of 99 (89%) patients in the bupivacaine group returned the questionnaire. Twelve patients in the mepivacaine group and two patients in the bupivacaine group were not satisfied with their spinal anaesthesia ($P<0.05$). Two patients who had received mepivacaine spinal anaesthesia had headache at home, one for 3 days and the other for 1 week. Neither needed an extradural blood patch. Two patients who had received bupivacaine spinal anaesthesia reported transient deterioration in hearing.

The incidence of transient neurological symptoms differed ($P<0.001$) between patients who received

Table 1 Characteristics of patients and variables of spinal anaesthesia (median (range) or number)

Characteristic/variable	4% Mepivacaine	0.5% Bupivacaine
n	100	100
Sex (M/F)	45/55	47/53
Age (yr)	41 (21–68)	44 (20–70)
Height (cm)	170 (148–191)	171 (150–193)
Weight (kg)	76 (49–115)	75 (50–116)
Needle size		
25-gauge	16	17
27-gauge	84	83
Patient position during injection		
Sitting	4	3
Lateral	96	97
Duration of operation (min)	32 (9–115)	32 (7–87)
Patient position during operation		
Supine	95	94
Lithotomy	2	4
Prone	3	2

Table 2 Details of the spinal anaesthetic procedures. ***$P<0.001$

	All patients		Patients with transient neurological symptoms	
	4% Mepivacaine	0.5% Bupivacaine	4% Mepivacaine	0.5% Bupivacaine
n	100	100	30***	3
Sex (M / F)	45/55	47/53	14/16	1/2
Surgery				
Arthroscopy of knee	67	58	22	2
Other orthopaedic	17	21	3	1
Varicose veins	13	15	3	0
Rectal or gynaecological	3	6	2	0
Attempts at dural puncture				
1	88	86	25	2
2–3	5	8	4	1
>3	7	6	1	0
Paraesthesia during dural puncture	6	5	2	0
Median maximum height of block (range)	T6 (T3–12)	T7 (T3–L4)	T6 (T3–12)	T8 (T8–12)

Table 3 Characteristics of the motor block (median (range)). Motor block 3=unable to move the feet or knees, 2=able to move the feet only, 1=just able to move the knees. ***$P<0.001$

	All patients		Patients with transient neurological symptoms	
	4% Mepivacaine	0.5% Bupivacaine	4% Mepivacaine	0 5% Bupivacaine
n	100	100	30***	3
Motor block				
3	96***	81	29	3
2	3	14	1	0
1	0	1	0	0
No paralysis	1	4	0	0
Time to maximum motor block (min)	8 (5–60)***	17 (5–60)	8 (5–60)	13 (5–60)
Time to total recovery of motor block (min)	135 (90–210)	127 (60–240)	130 (90–210)	100 (60–120)

Table 4 Nature of pain and analgesic requirement in patients with transient neurological symptoms (NSAID=non-steroidal anti-inflammatory drug). ***$P<0.001$

	4% Mepivacaine	0.5% Bupivacaine
n	30***	3
Location of pain		
Buttocks	13	0
Buttocks and thighs	13	1
Thighs	0	1
Buttocks, thighs and legs	4	1
Severity of pain		
Mild or moderate	20	3
Severe	10	0
Onset of pain after recovery of block (h)		
1–6	16	1
6–12	8	1
12–24	2	1
24–48	4	0
Duration of pain (h)		
<12	11	3
12–24	9	0
24–72	9	0
120	1	0
Needed analgesia		
Yes	23	2
NSAID	14	1
Opioids	1	0
Both NSAID and opioids	8	1
No	7	1

mepivacaine (30%) and those who had received bupivacaine (3%). The mean age of patients with transient neurological symptoms in the mepivacaine group was 44 (range 21–68) yr and in the bupivacaine group 51 (47–54) yr. Mean weight was 77 (56–105) kg in the mepivacaine group and 77 (75–80) kg in the bupivacaine group. There was no association between the incidence of transient neurological symptoms and patient sex, weight or age. All patients who experienced transient neurological symptoms had been in the supine position during operation, except for one who was in the lithotomy position. Furthermore, in all patients with transient neurological symptoms the spinal puncture had been performed in the lateral position. There was no association between transient neurological symptoms and difficulty of block placement or paraesthesia. In all three patients in the bupivacaine group and in 26 of 30 patients with symptoms in the mepivacaine group, pain occurred within the first 24 h. In one patient who had both pain and dysaesthesia in the buttocks, symptoms lasted for 5 days. In 14 patients in the mepivacaine group and in one patient in the bupivacaine group, pain was relieved by non-steroidal anti-inflammatory drugs; nine patients also needed opioids. Five patients reported that the pain was worse in the supine position and it was relieved when they stood up and started to walk (table 4).

No patient had sensory disturbances, change in muscle strength or difficulties in voiding on the first postoperative morning.

Three patients who had transient neurological symptoms after mepivacaine spinal anaesthesia had experienced similar symptoms before, one after 5% hyperbaric lignocaine spinal anaesthesia and two after 4% hyperbaric mepivacaine anaesthesia. All three patients who had transient neurological symptoms in the bupivacaine group returned the questionnaire and were satisfied with the spinal anaesthesia. In the mepivacaine group, 27 of 30 patients returned the questionnaire and 20% were not satisfied with spinal anaesthesia; four because of transient neurological symptoms, one because of painful puncture and one patient complained of difficulty in breathing because of the maximum height of block (T4) during operation.

All complaints were transient and had disappeared by the time the patients mailed the questionnaire.

Discussion

In this study, transient neurological symptoms occurred in 30% of patients who received spinal anaesthesia with mepivacaine but also in 3% of patients who received spinal anaesthesia with hyperbaric bupivacaine. However, duration of symptoms after bupivacaine spinal anaesthesia was less than 12 h compared with 12–120 h after mepivacaine spinal anaesthesia.

In 1993, Schneider and colleagues published the first case reports of transient neurological symptoms after spinal anaesthesia with 5% hyperbaric lignocaine.[1] Other later studies have shown similar symptoms, termed transient radicular irritation (TRI) after 5% hyperbaric lignocaine spinal anaesthesia in 10–37% of patients.[2–5] Thus the incidence of transient neurological symptoms or TRI after concentrated solutions of 4% mepivacaine and 5% lignocaine is similar. In the study of Pollock and colleagues the incidence of TRI was 16% after both

5% hyperbaric lignocaine and 2% lignocaine without glucose, but 0% after 0.75% hyperbaric bupivacaine.[5] In the study by Tarkkila, Huhtala and Tuominen, only one of 110 patients had TRI after 0.5% hyperbaric bupivacaine.[10] The neurotoxic potential of 5% hyperbaric lignocaine and 0.75% bupivacaine has been evaluated.[7] Exposure of amphibian nerves to 0.75% isobaric bupivacaine produced partially reversible conduction block, whereas 5% lignocaine with or without glucose caused irreversible block of impulses.[7] Furthermore, it has been shown in an *in vitro* study that lignocaine 80 mmol, which is equivalent to a concentration of 2% lignocaine, caused complete ablation of impulse activity.[8] In clinical studies, decreasing the concentration of lignocaine from 5% to 2% did not prevent the development of TRI.[5 15]

The doses of mepivacaine and bupivacaine in our study were based on the clinical study of Pitkänen, Kalso and Rosenberg, where 80 mg (2 ml) of 4% hyperbaric mepivacaine resulted in spinal anaesthesia similar to that after a dose of 0.5% hyperbaric bupivacaine 10 mg (2 ml) or 0.5% hyperbaric lignocaine 100 mg (2 ml).[14] Also, spinal anaesthesia with mepivacaine 60 mg produced analgesia and motor block of good quality but of short duration compared with spinal anaesthesia with 0.5% hyperbaric bupivacaine 15 mg.[16] Decreasing the dose of mepivacaine from 80 to 60 mg may diminish the development of transient neurological symptoms and still provide adequate anaesthesia for operations on the lower extremities.

Lambert, Lambert and Strichartz demonstrated synergistic neurotoxic effects of lignocaine and glucose *in vitro*, in frog sciatic nerve.[7] The loss of neural activity was not found to correlate with the glucose concentration and inhibition could not be induced without local anaesthetic. The hyperbaric mepivacaine solution has a higher concentration of glucose (95 mg ml^{-1}) compared with hyperbaric lignocaine (62.5 mg ml^{-1}) or hyperbaric bupivacaine (80 mg ml^{-1}). The greater the baricity of the solution the greater the chance of gravity-determined spread restriction. This, together with the use of small gauge pencil-point needles with one side hole near the tip, could result in pooling of the concentrated local anaesthetic solution. Repeated injections through thin intrathecal catheters may, therefore, result in cauda equina syndrome.[17] Beardsley and colleagues showed that sacral direction of the needle orifice and a slow injection rate with a Whitacre needle may be predisposing factors to transient neurological complications with 5% hyperbaric lignocaine.[18] However, other studies have failed to confirm this.[3 10] In contrast, in this study we injected via Quincke-type needles (orifice at the bevelled tip) and initial directional pooling of the local anaesthetic in the sacral region was unlikely.

In addition to a toxic effect of the local anaesthetic, the lithotomy position during surgery has been thought to be a possible cause of transient neurological symptoms.[1 4 10] The lithotomy position may contribute to transient neurological symptoms by stretching the cauda equina and sciatic nerves, thus decreasing the vascular supply and increasing vulnerability to injury. In our study, four patients in the bupivacaine group and two in the mepivacaine group were in the lithotomy position during surgery. Only one patient in the mepivacaine group had transient neurological symptoms starting 24–48 h after anaesthesia. However, transient neurological symptoms occurred in 22 patients undergoing arthroscopy of the knee. In our hospital, arthroscopy patients have both legs straight at the hip, and flexed 90° at the knee. The operative leg position is varied throughout surgery. The position and manipulation may contribute to neural stretching and thus to the development of transient neurological symptoms. Also, Pollock and colleagues found a higher incidence of transient neurological symptoms in patients undergoing arthroscopy than in those having inguinal hernia repair.[5]

Individual physical characteristics of patients may predispose to the development of transient neurological symptoms after spinal anaesthesia. Interestingly, in this study three patients who had transient neurological symptoms after mepivacaine spinal anaesthesia had experienced similar symptoms before, one after 5% hyperbaric lignocaine and two after 4% hyperbaric mepivacaine spinal anaesthesia. It has been shown that the anatomical configuration of the spinal column affects the spread of subarachnoid anaesthetic solutions that move under the influence of gravity.[19 20] Both lumbar lordosis and thoracic kyphosis differ between individuals, particularly with respect to the lowest point of the thoracic spinal canal.[21] Musculoskeletal disturbances in the back and leg symptoms cannot be totally excluded. We speculate that profound relaxation of the supportive muscles of the lumbar spine may result in straightening of the lordotic curve, and even transient spondylolisthesis, when the patient is lying on the operating table. This may be responsible in part for the radiating back symptoms which occurred after the intense motor block, observed during mepivacaine spinal block in particular.

In summary , the incidence of transient neurological symptoms was greater after spinal anaesthesia with 4% hyperbaric mepivacaine than after 0.5% hyperbaric bupivacaine. Patients were more satisfied with bupivacaine spinal anaesthesia. Except for a greater number of complete motor blocks after mepivacaine, spinal anaesthesia and recovery were similar after both agents. Therefore, hyperbaric 0.5% bupivacaine 10 mg can be recommended for minor operations on the lower extremities or lower abdomen lasting less than 90 min.

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Comparison of volume controlled with pressure controlled ventilation during one-lung anaesthesia

M. TUĞRUL, E. ÇAMCI, H. KARADENİZ, M. ŞENTÜRK, K. PEMBECİ AND K. AKPİR

Summary

Pressure controlled ventilation (PCV) is an alternative mode of ventilation which is used widely in severe respiratory failure. In this study, PCV was used for one-lung anaesthesia and its effects on airway pressures, arterial oxygenation and haemodynamic state were compared with volume controlled ventilation (VCV). We studied 48 patients undergoing thoracotomy. After two-lung ventilation with VCV, patients were allocated randomly to one of two groups. In the first group (n=24), one-lung ventilation was started by VCV and the ventilation mode was then switched to PCV. Ventilation modes were performed in the opposite order in the second group (n=24). We observed that peak airway pressure (P=0.000001), plateau pressure (P=0.01) and pulmonary shunt (P=0.03) were significantly higher during VCV, whereas arterial oxygen tension (P=0.02) was significantly higher during PCV. Peak airway pressure (Paw) decreased consistently during PCV in every patient and the percentage reduction in Paw was 4–35% (mean 16.1 (SD 8.4) %). Arterial oxygen tension increased in 31 patients using PCV and the improvement in arterial oxygenation during PCV correlated inversely with preoperative respiratory function tests. We conclude that PCV appeared to be an alternative to VCV in patients requiring one-lung anaesthesia and may be superior to VCV in patients with respiratory disease. (*Br. J. Anaesth.* 1997; **79**: 306–310).

Key words
Ventilation, one-lung. Ventilation, volume controlled. Ventilation, pressure controlled.

During one-lung anaesthesia, arterial hypoxaemia is a major concern.[1] Volume controlled ventilation (VCV) is the traditional method of performing one-lung anaesthesia in patients undergoing thoracic surgery and an increase in airway pressure is usually observed. If the method of ventilation involves excessive amounts of airway pressure, vascular resistance of the dependent lung may be increased because of compression of intra-alveolar vessels.[2] Thus high airway pressures of the dependent lung may counteract hypoxic pulmonary vasoconstriction in the non-dependent lung by diverting blood flow away from the ventilated lung, thereby increasing pulmonary shunt fraction.[3]

One-lung ventilation implies delivering the entire tidal volume into one lung, which may result in barotrauma of the dependent lung. In order to avoid high airway pressures, anaesthetists may ventilate the dependent lung with lower tidal volumes and higher ventilatory frequencies during one-lung anaesthesia. However, lower tidal volumes have been demonstrated to predispose the dependent lung to atelectasis and worsen arterial oxygenation.[4 5]

Pressure controlled ventilation (PCV) is an alternative mode of ventilation which is used widely in severe respiratory failure. PCV has been shown to improve arterial oxygenation and decrease peak airway pressure because of its decelerating inspiratory flow.[6] Uniform distribution of inspired gas with PCV is the major cause of better arterial oxygenation in patients with respiratory failure.[7–10]

We applied PCV to one-lung anaesthesia and examined its use as a tool to improve ventilatory management of patients undergoing thoracic surgery. In our study, PCV was used for one-lung anaesthesia and its effects on airway pressure, arterial oxygenation and haemodynamic state were compared with those produced by VCV.

Patients and methods

The study was approved by the University of Istanbul Ethics Committee and all patients gave informed consent. We studied 48 patients, ASA I–III, undergoing thoracotomy requiring one-lung ventilation. On the evening before surgery, spirometry (forced vital capacity (FVC) and forced expiratory volume in 1 s (FEV_1)) was performed in the sitting position. An arterial blood-gas sample was also obtained with the patient breathing air. Patients were excluded if they had a history of cardiac, hepatic or renal disease.

All patients were premedicated with diazepam 0.15 mg kg^{-1} orally, 1 h before arrival in the operating room. On admission to the operating room, i.v.

MEHMET TUĞRUL*, MD, EMRE ÇAMCI, MD, HAKAN KARADENİZ, MD, MERT ŞENTÜRK, MD, KAMIL PEMBECİ, MD, KUTAY AKPİR, MD, Department of Anaesthesiology and Intensive Care, University of İstanbul, İstanbul Medical Faculty, Türkiye.
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*Address for correspondence: İ.Ü. İstanbul Tip Fakültesi, Anesteziyoloji Anabilim Dali, 34390, Çapa, İstanbul, Türkiye.

and intra-arterial cannulae were inserted under local anaesthesia and an ECG was attached. After pre-oxygenation, anaesthesia was induced with fentanyl 2 $\mu g\ kg^{-1}$ and propofol 2–2.5 $mg\ kg^{-1}$; tracheal intubation was facilitated with vecuronium 0.1 mg kg^{-1}. The trachea was intubated with an Univent tracheal tube (Fuji Corp, Japan). The bronchial blocker of the Univent tube was inserted into the mainstem bronchus of the operative side guided by a fibreoptic bronchoscope and separation of the lungs was demonstrated by capnography.[11] With this method, the tracing from the end-tidal carbon dioxide analyser connected to the proximal end of the bronchial blocker of the Univent shows a typical respiratory waveform. As the bronchial blocker cuff is gradually inflated, a straight line on the waveform indicates that lung isolation has occurred.

After induction of anaesthesia a 7-F pulmonary artery catheter (Abbott, Criticare Systems, USA) was inserted via the right internal jugular vein. Isoflurane 1–1.5%, fentanyl 0.05–0.1 $\mu g\ kg^{-1}\ min^{-1}$ and vecuronium 0.03 mg kg^{-1} every 30 min were used for maintenance of anaesthesia. Fentanyl bolus doses of 50–100 μg and i.v. fluids were administered to maintain systemic arterial pressure within ±20% of pre-induction values. Oesophageal temperature was monitored throughout the procedure and maintained greater than 36.5 °C by a heating blanket (Biçakçilar, Turkey) placed under the patient.

Our study consisted of three steps. Two-lung ventilation (TLV) with VCV (TLV-VCV) was performed in the lateral decubitus position in all patients (Servo 900C, Siemens, Stockholm, Sweden). On initiation of one-lung ventilation, patients were allocated randomly to one of two groups. In the first group ($n=24$), one-lung ventilation was started by VCV (OLV-VCV) and the ventilation mode was then changed to PCV (OLV-PCV). The modes of ventilation were performed in the opposite order in the second group ($n=24$).

During TLV-VCV and OLV-VCV, patients' lungs were ventilated with a tidal volume of 10 ml kg^{-1} and ventilatory frequency was adjusted to maintain arterial carbon dioxide tension (Pa_{CO_2}) at 4.5–6 kPa. PCV was initiated with a peak airway pressure that provided a tidal volume of 10 ml kg^{-1}. Ventilatory frequency was adjusted to maintain Pa_{CO_2} at 4.5–6 kPa during OLV-PCV. With both PCV and VCV, we used a 25% inspiratory time and a 10% pause time. Inspiratory oxygen concentration (FI_{O_2}) was adjusted to 0.5 in air during two-lung ventilation and to 1.0 during one-lung ventilation. End-tidal concentrations of carbon dioxide and isoflurane were monitored using a Criticare 1100 (Criticare Inc, USA).

In accordance with data obtained from previous studies,[12 13] all measurements were made 30 min after initiation of the ventilation mode. All operations were performed by the same surgical team and the study was completed before any pulmonary vessels were ligated. Measurements were completed during the minutes in which the surgeons stopped compressing the operative lung.

The following variables were measured and recorded at the end of each period. Arterial and venous oxygen tensions and saturations (Pa_{O_2}, Sa_{O_2}, $S\bar{v}_{O_2}$), Pa_{CO_2} and haemoglobin (Hb) were analysed within 5 min using ABL 505 and OSM3 Hemoximeter (Radiometer, Copenhagen, Denmark). Heart rate (HR), mean arterial pressure (MAP), pulmonary artery pressure (MPAP), central venous pressure (CVP) and pulmonary artery occlusion pressure (PAOP) were recorded from the Criticare 1100 (Criticare Inc, USA). Deltran II transducers (Utah Medical, USA) were used to measure pulmonary arterial and systemic pressures. The zero reference was the mid-chest level and vascular pressures were measured at end-expiration. Cardiac output (CO) was measured by a thermodilution technique using injection of 10 ml of 0.9% saline at 0 °C (Abbott Criticare Systems, USA). The mean value of three measurements was obtained. Pulmonary shunt (Qs/Qt) was calculated from standard formulae.[14]

Peak airway pressure (Paw) and mean airway pressure (Pmaw) were recorded during each mode of ventilation. Inspiratory plateau was established by activating the inspiratory hold on the Siemens Servo 900C ventilator. Inspiratory plateau pressure (Pplt) was measured during the last 0.3 s of each hold manoeuvre.

We studied Pa_{O_2} data in order to identify which patients would benefit from OLV-PCV. The relationship between "individual Pa_{O_2} differences between OLV-PCV and OLV-VCV" and respiratory function tests was studied by linear regression analysis.

Data are presented as mean (SD). Paired Student's t test, ANOVA and chi-square test were used to test the significance of the differences between groups. Statistical significance was assumed at $P=0.05$.

Results

Patient data are shown in table 1. Mean values for ventilation, gas exchange and haemodynamic variables at each time are presented in tables 2 and 3. During one-lung ventilation, arterial hypoxaemia (Sa_{O_2} <90%) requiring reinflation of the collapsed lung did not occur in any patient.

Pa_{CO_2}, Sa_{O_2}, $S\bar{v}_{O_2}$, Hb, MAP, MPAP, PAOP, CVP and CO did not differ significantly between any of the ventilation modes.

Comparison of the OLV-VCV and OLV-PCV modes revealed significant differences in Paw, Pplt,

Table 1 Patient data. FVC=Forced vital capacity, FEV_1=forced expiratory volume in 1 s, Pa_{O_2}=arterial oxygen tension, Pa_{CO_2}=arterial carbon dioxide tension (mean (SD) [range] or number) ($n=48$)

Age (yr)	56 4 [30–78]
Weight (kg)	70.3 (11 5) [46–95]
Sex (M/F)	38/10
Right-left-sided thoracotomy	28/20
Lobectomy/pneumonectomy	29/19
Preoperative FVC (% predicted)	77.1 (15) [46–117]
Preoperative FEV_1 (% predicted)	76 8 (14) [43–112]
Preoperative Pa_{CO_2} (kPa)	5 (0.63) [3 95–6 7]
Preoperative Pa_{O_2} (kPa)	10.2 (1.12) [7.9–12.8]

Table 2 Ventilation and gas exchange data (mean (SD)). *P*aw=Peak airway pressure, *P*plt=plateau pressure, *P*maw=mean airway pressure, Pa_{O_2}=arterial oxygen tension, Sa_{O_2}=arterial oxygen saturation, Pa_{CO_2}=arterial carbon dioxide tension, Sv_{O_2}=mixed venous oxygen saturation, *Qs*/*Qt*=intrapulmonary shunt, TLV=two-lung ventilation, OLV=one-lung ventilation, PCV=pressure controlled ventilation, VCV=volume controlled ventilation. *$P<0.05$ compared with OLV-VCV, ***$P<0.001$ compared with OLV-VCV

	TLV-VCV	OLV-VCV	OLV-PCV
Tidal volume (ml)	708 (112)	714 (111)	710 (114)
*P*aw (cm H_2O)	21.4 (4.7)	28.3 (5.1)	23.65 (3.85)***
*P*plt (cm H_2O)	15.7 (3.8)	18.5 (4.2)	17.8 (3.7)*
*P*maw (cm H_2O)	6.7 (1.4)	7.8 (2)	7.95 (1.55)
Pa_{O_2} (kPa)	27.5 (7.9)	28.4 (15.6)	32.3 (14.4)*
Sa_{O_2} (%)	99.1 (0.98)	98.3 (3.1)	98.7 (2.1)
Pa_{CO_2} (kPa)	4.8 (0.77)	5.06 (0.87)	5.05 (0.9)
Sv_{O_2} (%)	80.7 (6.8)	81.2 (8.3)	81.4 (7.23)
Qs/*Qt* (%)	16.7 (6.2)	40.2 (10.1)	36.2 (10)*

Table 3 Haemodynamic data (mean (SD)). HR=Heart rate, MAP=mean arterial pressure, MPAP=mean pulmonary artery pressure, PAOP=pulmonary artery occlusion pressure, CVP=central venous pressure, CO=cardiac output, TLV=two-lung ventilation, OLV=one-lung ventilation, PCV=pressure controlled ventilation, VCV=volume controlled ventilation

	TLV-VCV	OLV-VCV	OLV-PCV
HR (beat min^{-1})	77.5 (11)	79.4 (9.8)	78.8 (10)
MAP (mm Hg)	94 (14)	92 (11)	92.7 (12)
MPAP (mm Hg)	18 (3.2)	18.6 (3)	19.1 (4.6)
PAOP (mm Hg)	15.1 (2.3)	15.5 (3.7)	15.7 (3.7)
CVP (mm Hg)	10.8 (3 7)	11.4 (3.6)	11.6 (3.6)
CO (litre min^{-1})	4.4 (0.9)	4.55 (0.8)	4.6 (0.87)

Pa_{O_2} and *Qs*/*Qt*. *P*aw was significantly lower during OLV-PCV than during OLV-VCV (23.65 (3.85) cm H_2O *vs* 28.3 (5.1) cm H_2O) ($P=0.000001$). Compared with OLV-VCV, *P*aw decreased consistently during OLV-PCV in every patient, ranging from 1 to 13.5 cm H_2O. The percentage *P*aw difference was 4–35% (mean 16.1 (8.4) %). *P*plt was also significantly lower during OLV-PCV than during OLV-VCV (17.8 (3.7) *vs* 18.5 (4.2) cm H_2O) ($P=0.01$) .

Mean Pa_{O_2} was significantly higher during OLV-PCV (32.3 (14.4) kPa *vs* 28.4 (15.6) kPa) ($P=0.03$) than during OLV-VCV. Arterial oxygenation improved in 31 patients with OLV-PCV and in 17 patients with OLV-VCV ($P=0.008$). Twenty-three of 31 patients (74%) who had an improved Pa_{O_2} value with OLV-PCV had an FVC lower than 77%, whereas only six of 17 (35%) patients who had an improved Pa_{O_2} with VCV had an FVC lower than 77% ($P=0.02$). Also, 19 of 31 patients (61%) whose Pa_{O_2} improved with OLV-PCV had an FEV_1 lower than 77%, whereas five of 17 (30%) patients whose Pa_{O_2} improved with OLV-VCV had an FVC lower than 77% ($P=0.07$). On the basis of linear regression analysis "individual Pa_{O_2} difference between OLV-PCV and OLV-VCV" showed a significant correlation with FVC ($r=-0.30$, $P=0.02$) (fig. 1), but no significant correlation with FEV_1 ($r=-0.24$, $P=0.09$).

Mean *Qs*/*Qt* was significantly higher during OLV-VCV (40.2 (10.1) *vs* 36.2 (10) %, $P=0.02$) than during OLV-PCV. *Qs*/*Qt* was found to be higher during OLV-VCV in 32 patients, whereas OLV-PCV resulted in higher *Qs*/*Qt* values in only 16 patients ($P=0.002$).

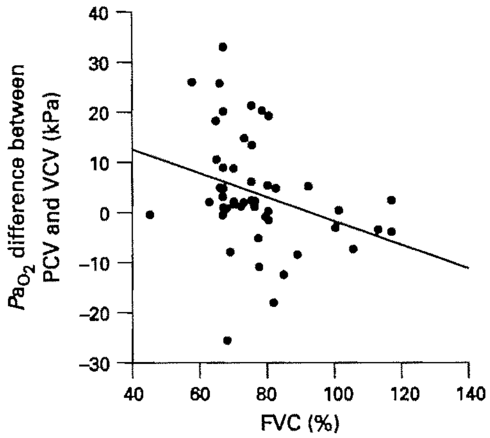

Figure 1 Individual Pa_{O_2} difference between PCV and VCV *vs* FVC (forced vital capacity) ($r=-0.30$, $P=0.02$) ($y=168.6-1.8x$).

Discussion

VCV is the common mode of ventilation used in patients undergoing one-lung anaesthesia. In our study, we performed pressure controlled ventilation to overcome some of the problems observed with one-lung anaesthesia. We planned to use almost the same tidal volumes to examine the effects of each mode on airway pressures, pulmonary shunt and arterial oxygenation. As tidal volumes greater than 10 ml kg^{-1} were reported to increase airway pressure and pulmonary vascular resistance in the dependent lung,[5 15 16] we chose a tidal volume of 10 ml kg^{-1} for the dependent lung which was reported to be least detrimental to arterial oxygenation.[17] As it has been documented previously that Pa_{O_2} tends to increase over 1 h after the onset of one-lung anesthesia,[18] we randomized the order of PCV and VCV.

High airway pressures may lead to barotrauma of the dependent lung.[19] It has been reported that high peak inspiratory pressure has some influence on the incidence of barotrauma[20] and avoiding high peak inspiratory pressures seems to be a safe form of ventilation.[21] In our study, peak inspiratory pressures were consistently lower during PCV. A reduction in peak inspiratory pressure of 4–35% induced by PCV is an advantage for one-lung anaesthesia.

It has been demonstrated previously that PCV is associated with sustained reductions in peak inspiratory pressure because of its decelerating flow profile.[7 8] In studies performed in patients with respiratory failure, peak inspiratory pressure was shown to decline from 38 to 33 cm H_2O[9] and from 43 to 40 cm H_2O[10] by PCV. The beneficial effects of reduced peak inspiratory pressures during PCV in terms of minimizing lung injury have been attributed to concomitant reductions in peak alveolar pressure and consequent decreases in alveolar distension.[22] However, there are no studies comparing the incidence of iatrogenic lung injury using PCV or VCV. It was postulated that the very rapid initial flows with PCV may cause different effects on filling patterns, and thus the risk of barotrauma from shearing may be less using pressure *vs* volume breaths.[23]

There is a growing tendency to define end-inspiratory plateau pressure as a more important determinant of barotrauma than peak airway pressure.[24] In our study, plateau pressure was found to be significantly lower during PCV. Furthermore, it is possible during VCV for some alveoli to receive higher pressures during inspiration than the end-inspiratory plateau pressure. In contrast, in no parts of the lung can the pressure be higher than the preset pressure during PCV.[22]

Because of the high peak inspiratory pressures usually observed with the initiation of one-lung anaesthesia, most anaesthetists tend to ventilate the dependent lung with lower tidal volumes and higher respiratory frequencies aiming to protect the dependent lung from hyperinflation. However, lower tidal volumes have been demonstrated to predispose the dependent lung to develop atelectasis, thereby worsening arterial oxygenation.[4,5] We assume that lower airway pressures obtained with PCV allow the use of higher tidal volumes during one-lung anaesthesia.

Factors that play a role in the hypoxaemia frequently seen during one-lung anaesthesia include reduction in dependent lung volume caused by induction of anaesthesia, abdominal and mediastinal compression, suboptimal positioning, low ventilation: perfusion ratios and atelectasis because of a high FI_{O_2}, and problems in removal of secretions.[25] Hypoxic pulmonary vasoconstriction is an autoregulatory mechanism that diverts blood flow away from hypoxic, atelectatic lung towards the remaining normoxic, ventilated lung and it is very effective in reducing hypoxic lung blood flow when the percentage hypoxic lung is intermediate (30–70%), that is the amount of lung that is hypoxic during one-lung anaesthesia.[26]

Compression of small intra-alveolar vessels during inflation of alveoli produces increased resistance to pulmonary blood flow in the dependent lung. This increase in vascular resistance may divert blood flow to the non-ventilated alveoli of the non-dependent lung. Further increases in tidal volume and airway pressure in the dependent lung are then unlikely to improve oxygenation and may make arterial oxygenation worse by diverting blood flow to the non-dependent lung.[4,16,17] Although not necessarily reflecting intra-alveolar pressure, the high peak and plateau pressures observed with VCV in our study may play a role in diverting blood flow to the non-dependent lung and produce a higher pulmonary shunt.

One of the aims of this study was to investigate the effects of PCV on arterial oxygenation during one-lung anaesthesia. It was demonstrated earlier that improvement in arterial oxygenation by PCV was not related to variations in mean airway pressure but resulted mostly from the beneficial effects of the decelerating inspiratory flow pattern produced by PCV on the distribution of gas within the lung.[7] In diseased lungs with different time constants, the decelerating flow of PCV sustains alveolar pressure longer than the constant flow of VCV, thereby aiding recruitment and improving homogenous distribution of inspired gas. In our study, Pa_{O_2} improved in most patients during PCV and mean Pa_{O_2} was significantly higher than that during VCV. The improvement in arterial oxygenation during PCV may be explained by the flow profile of this mode and also the lower pulmonary shunt obtained with PCV.

To answer the question "which patients benefited more from PCV" we investigated the correlation between individual Pa_{O_2} differences between PCV and VCV, and respiratory function tests. We found that there was a significant correlation between individual Pa_{O_2} difference between PCV and VCV, and FVC. Patients whose Pa_{O_2} improved with PCV generally had a poor FVC (fig. 1). Many of the studies demonstrating better arterial oxygenation with PCV compared with VCV were performed in patients with severe respiratory failure.[7–9] As may be expected, those patients who had dependent lung pathology of varying severity, especially patients with restrictive disease, benefited from the decelerating flow pattern of PCV which improved distribution of alveolar gas and arterial oxygenation.

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Acute effect of mitral valve replacement on extravascular lung water in patients receiving colloid or crystalloid priming of cardiopulmonary bypass

W. BUHRE, A. HOEFT, B. SCHORN, A. WEYLAND, M. SCHOLZ AND H. SONNTAG

Summary

Despite numerous studies on extravascular lung water (EVLW) in patients undergoing coronary artery bypass surgery, few data are available on the perioperative time course of EVLW in patients undergoing mitral valve replacement for mitral valve insufficiency (MVI). We have investigated 26 patients undergoing elective mitral valve replacement in order to determine the influence of the preoperative degree of mitral valve insufficiency (degree III or IV) and the effect of different priming solutions for cardiopulmonary bypass. Crystalloid priming with Ringer's lactate was compared with human albumin priming solution. Measurement of EVLW was performed using the thermo-dye dilution technique, before and 1, 6 and 24 h after surgery. Before operation, EVLW is increased significantly in patients with MVI degree IV (MVI-°IV) compared with patients with degree III (MVI-°III) and patients undergoing coronary artery bypass surgery. During the postoperative time course a significant decrease in EVLW was observed in patients with MVI-°IV whereas in patients with MVI-°III the amount of EVLW did not change. However, compared with patients undergoing coronary artery bypass surgery, EVLW remained above normal in both groups. There was no interaction between the type of priming solution and the postoperative time course of EVLW, and no differences in respiratory variables or duration of mechanical ventilation were observed between groups. (*Br. J. Anaesth.* 1997; **79**: 311–316).

Key words
Surgery, cardiovascular. Heart, cardiopulmonary bypass. Measurement techniques, indication dilution. Fluid therapy.

Contact of blood with tubing surface material of the cardiopulmonary bypass (CPB) during open heart surgery causes activation of several mediator systems.[1 2] The resulting systemic inflammatory response leads to increased capillary permeability and may cause impairment of myocardial function.[3–6] Therefore, pulmonary oedema is a typical complication after open heart surgery, in particular if a pure crystalloid solution is used for priming the cardiopulmonary bypass.[3 5 7]

In a previous study, we demonstrated that priming of cardiopulmonary bypass with nearly physiological colloid–osmotic pressure attenuated the increase in extravascular lung water (EVLW) compared with a pure crystalloid priming solution in patients undergoing coronary bypass surgery.[8] However, only moderate increases in EVLW were observed in the crystalloid group and pulmonary function variables did not differ between groups.[8] Because of costs, it is therefore questionable to advocate albumin priming for all patients. However, we hypothesized that patients who have additional risk factors for postoperative pulmonary dysfunction may benefit from colloid priming of cardiopulmonary bypass. A group of patients at risk of postoperative pulmonary complications are those with mitral valve insufficiency (MVI) undergoing mitral valve replacement.

Therefore, the aim of this study was to compare the effect of a priming solution with nearly physiological colloid–osmotic pressure (4% albumin) with a pure crystalloid priming solution (Ringer's lactate) on postoperative EVLW content in patients undergoing mitral valve replacement.

Patients and methods

We studied 26 patients undergoing elective surgery for mitral valve replacement. The study was approved by the local Ethics Committee and patients gave fully informed consent. Twelve patients presented with angiographic determined mitral valve insufficiency degree three (MVI-III°, regurgitation fraction >30–50% of stroke volume) and 14 patients with mitral valve insufficiency degree four (MVI-IV°, regurgitation fraction >50% of stroke volume). Patients were allocated randomly to subgroups with a different priming volume for

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W. BUHRE*, MD, A. WEYLAND, MD, H. SONNTAG, MD, Zentrum Anaesthesiologie, Rettungs- und Intensivmedizin der Universitat Gottingen, Robert-Koch-Str 40, D-37075 Gottingen, Germany. A. HOEFT, MD, M. SCHOLZ, MD, Klinik und Poliklinik fur Anästhesiologie und spezielle Intensivmedizin der Universitat Bonn, Sigmund Freud Str 25, D-53105 Bonn, Germany. B. SCHORN, MD, Klinik und Poliklinik fur Thorax-, Herz und Gefäßchirurgie der Universität Gottingen, Robert-Koch-Str 40, D-37075 Gottingen, Germany. Accepted for publication. March 25, 1997.

*Address for correspondence: Zentrum Anaesthesiologie, Rettungs- und Intensivmedizin der Universitat Gottingen, Robert-Koch-Str. 40, D-37075 Gottingen, Germany.

cardiopulmonary bypass. Consequently, two subgroups (MVI-III°-HA, $n=6$ and MVI-IV°-HA, $n=7$) received a priming volume with near physiological colloid–osmotic pressure. The priming solution consisted of 400 ml of 20% human albumin (HA), Ringer's lactate 1000 ml, 5% glucose 500 ml and bicarbonate 100 ml, resulting in an effective albumin concentration of 4%. The two other subgroups (MVI-III°-RL, $n=6$ and MVI-IV°-RL, $n=7$) received a pure crystalloid priming solution (Ringer's lactate 1400 ml, 5% glucose 500 ml and bicarbonate 100 ml). Cardiopulmonary bypass was performed under conditions of moderate hypothermia (nasopharyngeal temperature 32 °C), and ice-cooled crystalloid cardioplegic solution was used for myocardial protection.

Premedication comprised flunitrazepam 1–2 mg orally on the evening before surgery and also 1 h before arrival in the operating room. After arrival in the anaesthesia induction room, ECG leads II and V5 were attached. A central venous catheter was inserted under local anaesthesia and a 5-F introducer sheet was placed into the right femoral artery for measurement of arterial pressure. General anaesthesia was induced with fentanyl 7 μg kg^{-1} and etomidate 0.3 mg kg^{-1}. Pancuronium 0.1 mg kg^{-1} was given to facilitate tracheal intubation. Tidal volume and inspired fraction of oxygen (FI_{O_2}) were adjusted to maintain normal levels of arterial partial pressure of carbon dioxide (Pa_{CO_2}) and an arterial oxygen saturation (Sa_{O_2}) greater than 95%. Anaesthesia was maintained with fentanyl 6–7 μg kg^{-1} h^{-1} and midazolam 90–105 μg kg^{-1} h^{-1}.

After induction of anaesthesia a 7-F pulmonary artery catheter was introduced into the pulmonary artery via the right internal jugular vein. Additionally, a combined 4-F fibreoptic–thermistor catheter was inserted via the introducer sheet in the femoral artery and advanced 40 cm up the thoracic aorta. Special care was taken to confirm that the position of the catheters did not change during the study. The fibreoptic–thermistor catheters were connected to a commercially available optoelectronic device (Pulsion-COLD system, Pulsion, Munich, Germany) which allows simultaneous detection of thermo- and dye-dilution curves.

Haemodynamic and indicator dilution measurements were performed after induction of anaesthesia and at 1, 6 and 24 h after surgery. Arterial and mixed venous blood samples were obtained for measurement of haemoglobin content, oxygen saturation (OSM-3 haemoximeter, Radiometer, Copenhagen, Denmark) and blood-gas analysis (IL 1302 pH/blood-gas analyser, Instrumentation Laboratory Inc., Lexington, MA, USA). Standard haemodynamic variables (heart rate, arterial, central venous and pulmonary artery arterial pressures) were obtained. Measurements were performed when a steady state condition had been verified for at least 5 min.

Measurements of indicator dilution curves were obtained by triple bolus injections of 10 ml of ice-cooled indocyanine green dye (ICG) 1.25 mg ml^{-1} into the right atrium. Injections were spread randomly over the respiratory cycle. The resulting aortic dye dilution curve and also the two thermodilution curves obtained in the pulmonary artery and aorta were digitized and stored on hard disk (Pulsion COLD system, Fa Pulsion, Munich, Germany).

Extravascular lung water (EVLW) was calculated according to the following formula:

$$\mathrm{EVLW}=\frac{\mathrm{CO}\cdot(\mathrm{mtt}_{\mathrm{cent-thermo}}-\mathrm{mtt}_{\mathrm{cent-dye}})}{\mathrm{BW}} \qquad (1)$$

where CO=cardiac output (litre min^{-1}), $\mathrm{mtt}_{\mathrm{cent-thermo}}$=mean transit time of negative heat between the pulmonary artery and aorta (s), $\mathrm{mtt}_{\mathrm{cent-dye}}$=mean transit time of indocyanine green dye between the pulmonary artery and aorta (s) and BW=body weight (kg).

Cardiac output was calculated from the area under the thermodilution curve (Stewart–Hamilton method). Calculation of mean transit time ($\mathrm{mtt}_{\mathrm{cent-thermo}}$, $\mathrm{mtt}_{\mathrm{cent-dye}}$) requires exclusion of recirculating indicator from the dye- and thermodilution curves.[7 8] Conventionally, mathematical exclusion of recirculation is accomplished by mono-exponential extrapolation of the downslope of the indicator dilution curve between 70 and 30% of maximum height.[8 9] It has been demonstrated by our group that this approach carries a systematic error for thermodilution measurements, which leads to overestimation of $\mathrm{mtt}_{\mathrm{cent-thermo}}$ because of incomplete elimination of recirculation and insufficient exclusion of pre-pulmonary thermo-accessible volume.[8 9] Therefore, in this study we used an alternative approach which is based on stochastical analysis, as suggested by Böck and colleagues.[9] The mathematical background of this technique has been described in detail in previous publications by our group and also by others.[8–11]

Briefly, the relation between the output (aortic indicator dilution curve) and input (pulmonary indicator dilution curve) of the system can be described mathematically by a convolution integral (eqn (2)):

$$C_{ao}(t)=\int_{0}^{t} h(t-u)\cdot C_{\mathrm{pulm}}(u)d(u) \qquad (2)$$

whereas C_{ao} (t)=calculated concentration–time course of an aortic indicator dilution curve (output) depending on the concentration–time course of the indicator measured in the pulmonary artery (C_{pulm}) (input).[8] The pulmonary transport function (h (t)) characterizes the indicator dispersion during passage through the lung. In this study, aortic and pulmonary thermodilution curves were measured, and the pulmonary transport function (h (t)) was calculated from these curve.[8] Basically, the pulmonary transport function was determined by iterative convolution of the pulmonary artery thermodilution curve with a lagged normal density function using a non-linear least square algorithm.[8] The advantage of this approach is that determination of mean transit time ($\mathrm{mtt}_{\mathrm{cent-thermo}}$) through the pulmonary circulation is independent of recirculating indicator as the mean transit time is a variable of transport function.[9 10] In a previous study[8] we applied the convolution technique for both indicators, thermal and dye, but analysis of the data revealed that $\text{mtt}_{\text{cent-dye}}$ values did not differ significantly if elimination of systemic recirculation was performed by monoexponential extrapolation or by the deconvolution approach.[12] Therefore, in this study pulmonary measurements of the dye curves were not deemed necessary as elimination of recirculation could be performed adequately by monoexponential extrapolation of the aortic dye curves.

STATISTICAL ANALYSIS

All data are presented as mean (SD). Two-tailed Student's *t* test for unpaired data were used to compare biometric data and data on cardiopulmonary bypass and ischaemic arrest. The effects of colloid compared with crystalloid priming and the effect of mitral valve insufficiency (MVI-°III compared with MVI-°IV) were tested by two-way analysis of variance for repeated measurements (ANOVA, Statistica Ver. 3.1, Statsoft Inc.). $P \leqslant 0.05$ was considered significant. *Post-hoc* testing within each group and between groups was performed when a significant interaction between repeated measures factor and type of priming solution or degree of mitral valve failure was found. Tukey HSD test was used for *post-hoc* comparison and $P < 0.05$ was considered significant.

Results

There were no significant differences between groups in biometric data, duration of heart arrest and time until tracheal extubation (table 1). Pooled cardiopulmonary data for patients with degree III or IV mitral valve insufficiency and for crystalloid or colloid priming of the cardiopulmonary bypass are presented in tables 2 and 3 and figure 1.

There were no significant differences between groups or subgroups for any of the haemodynamic variables. Heart rate, central venous pressure and cardiac index increased significantly at 1, 6 and 24 h after surgery (tables 2, 3). Mean arterial pressure (MAP) increased slightly 1 and 24 h after surgery. Pulmonary capillary wedge pressure did not

Table 1 Patient data and data on cardioplegic arrest, extracorporeal circulation and ischaemic arrest in patients with mitral value failure (MVF) degree II or IV, receiving either crystalloid (RL) or colloid (HA) priming. Data are (mean (SD or range) or number). No significant differences

	MVF-HA (*n*=13)	MVF-RL (*n*=13)	MVF-III° (*n*=12)	MVF-IV° (*n*=14)
Sex (M/F)	8/6	5/9	7/7	6/8
Age (yr)	63.2 (55–74)	58.7 (36–71)	62.4 (49–71)	60.2 (36–74)
Body surface area (m^2)	1.80 (0.14)	1.76 (0.13)	1.83 (0.12)	1.75 (0.15)
Body weight (kg)	68.6 (9.18)	67.4 (8.31)	72.6 (9.66)	66 0 (10.2)
Time of perfusion (min)	102 (32)	99 (40.9)	106 (38)	93 (31)
Time of ischaemia (min)	64 (12)	65 (28)	72 (24)	61 (20)
Time to extubation (h)	17.4 (6.6)	14.9 (4.9)	16.9 (4.1)	16.0 (6.4)
Degree III/IV of mitral valve insufficiency	6/7	6/7		

Table 2 Haemodynamic data for patients during the perioperative time course. All data are mean (SD) for patients with mitral valve insufficiency (MVI) degree III or IV, receiving either crystalloid (RL) or colloid (HA) priming. HR=Heart rate, MAP=mean arterial pressure, PCWP=pulmonary capillary wedge pressure, CVP=central venous pressure. A=After induction of anaesthesia (control); 1 h, 6 h and 24 h=1, 6 and 24 h after surgery. *$P < 0.05$, **$P \leqslant 0.01$ compared with after induction of anaesthesia.

Group	Time	HR (beat min^{-1})	MAP (mm Hg)	PCWP (mm Hg)	CVP (mm Hg)
MVI-III°-RL	A	68 (17)	76 (10)	19 (4)	7 (4)
(*n*=6)	1 h	101 (12)*	78 (9)	16 (4)	11 (2)**
	6 h	92 (7)*	79 (8)	16 (6)	11 (3)**
	24 h	85 (15)*	84 (19)	21 (5)	14 (2)**
MVI-III°-HA	A	63 (10)	81 (20)	14 (4)	7 (4)
(*n*=6)	1 h	87 (15)*	88 (14)**	16 (5)	11 (3)**
	6 h	94 (13)*	75 (10)	13 (4)	11 (3)**
	24 h	80 (13)*	83 (17)**	15 (2)	14 (2)**
MVI-IV°-RL	A	58 (9)	70 (4)	19 (4)	7 (4)
(*n*=7)	1 h	100 (22)*	83 (7)**	15 (5)	12 (4)**
	6 h	78 (13)*	71 (12)	15 (5)	13 (3)**
	24 h	79 (15)*	83 (11)**	15 (4)	13 (4)**
MVI-IV°-HA	A	64 (11)	70 (10)	18 (6)	7 (2)
(*n*=7)	1 h	93 (18)*	86 (13)**	18 (7)	9 (3)*
	6 h	81 (15)*	69 (9)	17 (4)	10 (4)**
	24 h	83 (14)*	80 (12)**	16 (3)	11 (4)**
Pooled data	A	63 (11)	74 (12)	17 (6)	7 (3)
(*n*=26)	1 h	95 (17)**	84 (11)**	16 (5)	11 (4)**
	6 h	86 (13)**	73 (10)	16 (4)	12 (4)**
	24 h	81 (14)**	82 (12**)	16 (4)	13 (3)**
Repeated measures factor		$P \leqslant 0.01$	$P \leqslant 0.01$	ns	$P \leqslant 0.01$
Time course *vs* degree of MVI		ns	ns	ns	ns
Time course *vs* priming of CPB		ns	ns	ns	ns

Table 3 Data on cardiac index (CI), stroke volume index (SVI), central blood volume (CBV), Pa_{O_2}/FI_{O_2} ratio and extravascular lung water (EVLW). Data are mean (SD) for patients with mitral valve insufficiency (MVI) degree III or IV, receiving either crystalloid (RL) or colloid (HA) priming. A=After induction of anaesthesia (control); 1 h, 6 h and 24 h=1, 6 and 24 h after surgery. $^*P<0.05$, $^{**}P<0.01$ compared with after induction of anaesthesia

Group	Time	CI (litre $min^{-1} m^{-2}$)	SVI (ml)	Pa_{O_2}/FI_{O_2} (mm Hg)	EVLW (ml kg^{-1})
MVI-III°-RL	A	2.5 (0.5)	38 (6)	330 (110)	7.8 (2.6)
(*n*=6)	1 h	3.0 (0.6)*	30 (7)*	306 (110)	7.2 (2.5)
	6 h	3.9 (0.8)*	42 (8)	310 (45)	7.5 (3.3)
	24 h	3.4 (0.7)*	39 (7)	239 (28)**	7.9 (3.8)
MVI-III°-HA	A	2.0 (0.4)	32 (8)	305 (108)	7.4 (1.4)
(*n*=6)	1 h	2.9 (1.4)*	33 (14)	374 (63)	8.0 (1.5)
	6 h	3.2 (1.3)*	34 (13)	320 (116)	7.6 (2.0)
	24 h	3 4 (0.4)*	43 (6)	241 (88)**	8.6 (4.5)
MVI-IV°-RL	A	2.6 (0.7)	46 (13)	338 (138)	13.0 (8.7)
(*n*=7)	1 h	2.7 (0.6)	28 (6)*	346 (92)	8.7 (2.8)**
	6 h	3.0 (0.6)*	39 (10)	303 (73)	9.8 (3.1)**
	24 h	2.5 (0.4)	32 (6)	240 (46)**	9.2 (3.8)**
MVI-IV°-HA	A	2.5 (0.7)	40 (8)	348 (88)	14.1 (3.3)
(*n*=7)	1 h	3.2 (0.7)*	36 (10)	294 (58)	10.4 (2.7)**
	6 h	3.5 (0.7)*	44 (10)	274 (71)	8.6 (2.6)**
	24 h	3.4 (0.5)*	41 (4)	230 (67)**	9.1 (2.8)**
Pooled data	A	2.4 (0.6)	39 (10)	345 (111)	10.8 (3.9)
(*n*=26)	1 h	3.0 (0.9)*	32 (10)*	313 (98)	8.6 (2.6)**
	6 h	3.4 (0.9)**	40 (11)	310 (99)	8.5 (2.8)**
	24 h	3.1 (0.6)**	39 (7)	240 (59)**	8.7 (3.5)**
Repeated measures-factor		$P\leqslant0.01$	$P\leqslant0.05$	$P\leqslant0.01$	$P\leqslant0.01$
Time course *vs* degree of MVI		ns	ns	ns	$P\leqslant0.01$
Time course *vs* priming of CPB		ns	$P\leqslant0.01$	ns	ns

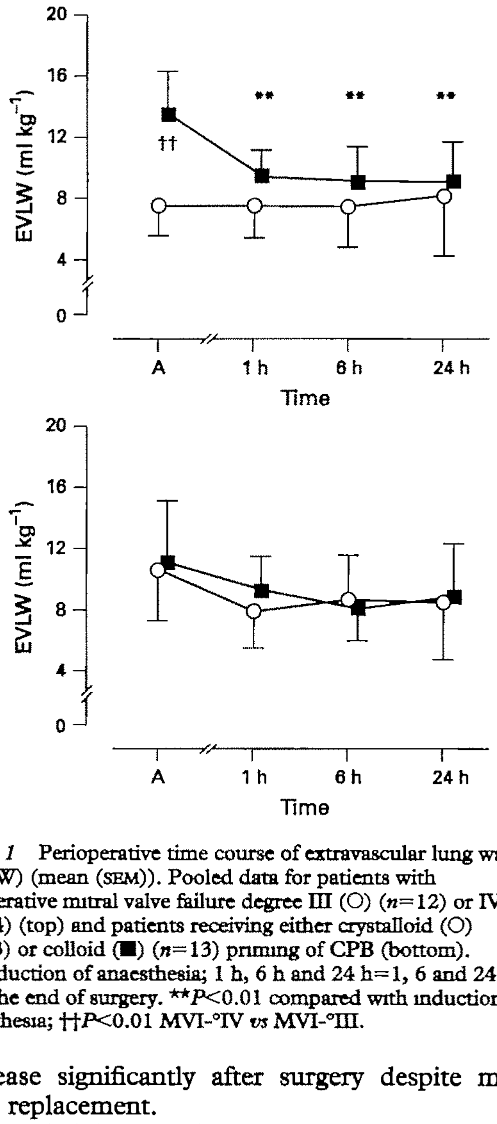

Figure 1 Perioperative time course of extravascular lung water (EVLW) (mean (SEM)). Pooled data for patients with preoperative mitral valve failure degree III (○) (*n*=12) or IV (■) (n=14) (top) and patients receiving either crystalloid (○) (*n*=13) or colloid (■) (*n*=13) priming of CPB (bottom). A=Induction of anaesthesia; 1 h, 6 h and 24 h=1, 6 and 24 h after the end of surgery. $^{**}P<0.01$ compared with induction of anaesthesia; ††$P<0.01$ MVI-°IV *vs* MVI-°III.

decrease significantly after surgery despite mitral valve replacement.

In pooled data, stroke volume index decreased 1 h after surgery (table 3). The decrease occurred mainly in patients receiving a crystalloid priming for the extracorporeal circuit and was statistically significant only for this group despite the degree of mitral valve insufficiency (table 3). After initial fluid replacement in the intensive care unit, SVI reached preoperative values 6 h after operation (table 2).

As expected, EVLW increased in all patients before surgery, compared with values in patients undergoing coronary artery bypass surgery (10.8 (3.9) *vs* 3.6 (1.0) ml kg^{-1}).[8] Moreover, there was a significant difference in EVLW between patients with mitral valve disease of degree III or IV (7.6 (2.0) *vs* 13.6 (2.9) ml kg^{-1}; $P<0.01$) (fig. 1, table 3). EVLW decreased significantly in the subgroup of patients with mitral valve failure degree IV ($P<0.01$, fig. 1), whereas values remained unchanged in patients with mitral valve failure degree III (fig. 1, table 3). In both groups of patients, EVLW values remained above normal compared with patients undergoing coronary artery bypass surgery.[8 12] The type of priming solution for cardiopulmonary bypass did not influence the postoperative time course of EVLW (fig. 1, table 3).

Pre- and postoperative Pa_{O_2}/FI_{O_2} ratios did not differ in patients with MVI-°III compared with those with MVI-°IV (table 3). After extubation, a significant decrease in Pa_{O_2}/FI_{O_2} ratio was observed, but there was no interaction between type of priming volume and Pa_{O_2}/FI_{O_2} ratio. The time to tracheal extubation did not differ between groups or subgroups of patients (table 1).

Discussion

We have demonstrated that EVLW was increased before operation in patients with mitral valve insufficiency compared with patients undergoing coronary artery bypass surgery.[7 8] The amount and perioperative time course of EVLW depended primarily on the degree of mitral valve insufficiency, whereas there was no significant influence of the type of priming solution on the postoperative time course of EVLW.

Accumulation of EVLW in patients after cardiopulmonary bypass has been described by several authors. However, most of these studies were performed in patients undergoing coronary artery bypass surgery.[7 8 13–18] Despite different measurement techniques and a wide range of absolute values, postoperative changes in EVLW were comparable in most studies, that is EVLW accumulation occurred mainly during the first 6 h after surgery.[7 8 14–18]

Mitral valve insufficiency leads to regurgitation of blood which may influence the shape of the aortic indicator dilution curve. For instance, it is well known that tricuspid valve insufficiency may lead to a systematic error in the assessment of cardiac output obtained in the pulmonary artery.[19 20] In this study, tricuspid insufficiency was excluded by preoperative echocardiographic examinations in all patients. Interestingly, there was good agreement for cardiac output values determined from pulmonary and aortic thermodilution curves. Obviously, the presence of mitral valve insufficiency does not necessarily affect determination of cardiac output values from aortic indicator dilution curves.

As described by Hoeft and colleagues[8] and Mehlhorn and colleagues[12] in more detail, the double indicator dilution technique with only a single site of measurement and monoexponential extrapolation of tracer curves leads to overestimation of EVLW. Therefore, in our investigation the convolution approach with two sites of measurements and simultaneous detection of thermodilution curves in the pulmonary artery and aorta was used for calculation of the pulmonary transport function of the thermal indicator.[9 10] Using this method, mean transit time can be calculated on the basis of the pulmonary transport function, and errors caused by insufficient elimination of recirculation can be avoided.[8–10]

Another possible source of error in the determination of EVLW could be the dependency of the calculated values from actual cardiac output. Wickerts and co-workers have demonstrated that the dependency of EVLW from cardiac output is not present when a system with combined, simultaneous fibreoptic–thermistor catheters is used.[21] Therefore, the dependency of EVLW measurements from cardiac output was a problem associated with the first generation of "lung water computers" which used an extracorporeal densitometer for dye detection.[21 22]

Hoeft and colleagues showed that addition of albumin in a sufficiently high concentration to the priming solution of the cardiopulmonary bypass attenuates accumulation of EVLW after CPB in patients undergoing coronary artery bypass surgery.[8] However, the clinical significance of this finding is unclear because the small differences in lung water accumulation between groups were not associated with differences in pulmonary function variables in the study of Hoeft and colleagues.[8] In a study by Hachenberg and co-workers in patients undergoing coronary artery bypass surgery, oxygenation was moderately impaired, as indicated by an increase in the alveolar–arterial oxygen gradient and increased venous admixture. Changes in gas exchange and EVLW do not correlate.[7] Until now, it seems questionable—mainly because of cost—if the use of high colloid priming solutions should be advocated in patients without preoperative pulmonary dysfunction.[7 8] Thus we examined the hypothesis that in patients with suspected pre-existing pulmonary oedema caused by mitral valve insufficiency, a colloid priming solution could have beneficial effects on the postoperative accumulation of lung water and gas exchange. To our knowledge, there is no other study available in which the effects of mitral valve replacement on EVLW have been investigated using the convolution technique.

Our results suggest that the postoperative time course of EVLW in patients depends mainly on the preoperative degree of mitral valve failure and not on the type of priming volume. Whereas in patients with MVI-IV° EVLW decreased significantly after surgery, it remained unchanged in patients with MVI-III°, but was still above normal compared with patients undergoing coronary artery bypass surgery.[8] The finding that EVLW values did not completely resolve immediately after surgery might be explained by possible remodelling of the connective tissue of the pulmonary vascular bed, which has been exposed to increased pulmonary pressure and chronic pulmonary oedema over a prolonged time.[23 24] To our knowledge no long-term investigations of EVLW after mitral valve replacement are available. Thus it remains unclear when, if ever, EVLW returns to normal values in these patients; however, we know that during the first 24 h after mitral valve replacement, EVLW is not normal.

Despite increased EVLW, the time to tracheal extubation did not differ between groups or subgroups of patients. As demonstrated by the time course of the Pa_{O_2}/FI_{O_2} ratio, no significant differences occurred despite an increase in EVLW. Therefore, our data suggest that increased EVLW values do not necessarily influence global variables of gas exchange in patients after mitral valve replacement.

In summary, we conclude that the preoperative degree of mitral valve insufficiency was more important for the postoperative time course of EVLW than the type of priming solution. Thus, in contrast with a previous study,[8] we could not demonstrate benefit of a high colloid priming solution with respect to the postoperative time course of EVLW or gas exchange in this group of patients.

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Acute normovolaemic haemodilution decreases postoperative allogeneic blood transfusion after total knee replacement

D. OLSFANGER, B. FREDMAN, B. GOLDSTEIN, A. SHAPIRO AND R. JEDEIKIN

Summary

We hypothesized that the success of postoperative blood conservation after acute normovolaemic haemodilution (NVHD) is influenced by the extent of intraoperative bleeding and surgical trauma, and the timing of autologous blood transfusion. As total knee replacement is associated with minimal intraoperative but extensive postoperative blood loss, this procedure is ideally suited to acute NVHD. Therefore, to test our hypothesis, 30 patients undergoing elective total knee replacement were enrolled in a prospective, randomized, controlled study. In groups NVHD-2 and NVHD-6, before induction of anaesthesia patients were bled to a target packed cell volume (PCV) of 28–30%, and in the post-anaesthesia care unit autologous blood was transfused over a 2-h period terminating after operation at 2 and 6 h, respectively. In the control group, NVHD was not performed. After operation, platelets, fibrinogen, prothrombin and partial thromboplastin time, and liver function, urea and electrolytes were measured and compared with preoperative baseline values. Significantly ($P<0.024$) more allogeneic blood was transfused in the control group (21 u.) compared with either group NVHD-2 (7 u.) or group NVHD-6 (5 u.). In the control group, despite the allogeneic blood transfusion, postoperative PCV decreased until day 4 after operation. Coagulation profile, liver function and urea and electrolytes concentrations were unaffected by the method of treatment. We conclude that for total knee replacement, acute NVHD is an effective blood conservation strategy. However, there was no difference in allogeneic blood administration between the two NVHD groups. Coagulation and liver function, and urea and electrolyte concentrations were unaffected by treatment. (*Br. J. Anaesth.* 1997; **79**: 317–321).

Key words
Blood, transfusion. Transfusion, autotransfusion. Blood, haemodilution. Surgery, orthopaedic.

Before administering blood to the surgical patient the sample must be collected, stored and screened for infectious disease and donor–recipient compatibility. This complex process requires a costly organizational infrastructure.

Despite rigorous screening procedures, inadvertent transmission of infectious diseases remains a significant cause of patient morbidity and mortality.[1–7] Furthermore, the increase in life expectancy has adversely affected the ratio of recipients to healthy donors and consequently decreased the availability of allogeneic blood.[8]

In an attempt to conserve natural blood products, curtail financial expenditure, prevent inadvertent transmission of infectious diseases and ensure safe blood transfusion in addition to simplifying the pre-administration process, alternative transfusion methods have been sought. While haemoglobin solutions,[9] perfluorocarbons and liposome-encapsulated haemoglobin have been developed, these compounds are expensive, have a limited circulatory half-life and do not replace the immunological or coagulant functions of natural blood products.[10] Similarly, preoperative autologous blood donation has been shown to be an expensive blood conservation technique.[11 12] Furthermore, because of administrative errors, incompatible blood transfusion may occur.[13 14]

In the surgical context, acute normovolaemic haemodilution (NVHD) is a potentially useful blood conservation strategy.[15] Because autologous blood is ultimately transfused, this simple technique does not require compatibility testing and is not associated with infectious disease transmission. However, as few randomized, prospective, controlled studies have been performed, the efficacy of NVHD in reducing administration of allogeneic blood is the subject of much debate.[16–19]

In our clinical experience, the extent of intraoperative bleeding and surgical trauma, and the timing of autologous blood transfusion directly influence the success of NVHD as a blood conservation strategy. While we have shown that NVHD for scoliosis surgery decreases allogeneic blood requirements both during and after operation,[15] we hypothesize that the extent of intraoperative blood loss during this surgical procedure adversely

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DAVID OLSFANGER, MB, CHB, BRIAN FREDMAN, MB, BCH, BERNARDO GOLDSTEIN, MD, ARIE SHAPIRO, MD, ROBERT JEDEIKIN*, BSC, MB, CHB, FFA(SA), Department of Anesthesiology and Critical Care, Meir Hospital, Kfar Sava, The Sackler School of Medicine, Tel Aviv University, Tel Aviv, Israel. Accepted for publication: April 18, 1997.

*Address for correspondence: Department of Anesthesiology and Critical Care, Meir Hospital, Kfar Sava 44281, Israel.

influences the success of NVHD as a blood conservation strategy. Unlike scoliosis surgery, total knee replacement is performed with an occlusive tourniquet and is associated with minimal intraoperative but extensive postoperative blood loss. As a result, total knee replacement is ideally suited to evaluate the efficacy of acute NVHD on postoperative blood administration. Therefore, we designed a study to determine the effect of NVHD on postoperative allogeneic blood administration after total knee replacement. In addition, we assessed the optimal transfusion time and effect of NVHD on coagulation factors, liver function, and urea and electrolyte concentrations.

Patients and methods

After obtaining Institutional Review Board approval, we studied 30 healthy, ASA I–III patients undergoing elective total knee replacement in a randomized, prospective, controlled, open label design. Patients with a history of ischaemic heart disease, hypertension, chronic renal failure, liver cirrhosis, bleeding disorders or current anticoagulant therapy were excluded.

On arrival in the operating room holding area, the radial artery was cannulated and monitoring equipment attached. Throughout the perioperative period the following variables were recorded at 1–5-min intervals: intra-arterial pressure, electrocardiogram (ECG) and peripheral haemoglobin oxygen saturation (Sp_{O_2}). Thereafter, according to a randomization table, patients were allocated to one of three groups: in groups NVHD-2 and NVHD-6, while in the operating room holding area patients were bled via a 16-gauge needle placed in the antecubital fossa to a target packed cell volume (PCV) of 28–30% using standard blood collection sets containing citrate–phosphate–glucose with adenine (CPDA-1; Travenol Laboratories Ltd, Israel). PCV was calculated using a Technicon H2 (Bayer) blood analyser. Blood volume was maintained with lactated Ringer's solution in a 1:3 (blood:Ringer's) replacement ratio such that arterial pressure and heart rate remained unchanged. The volume of blood removed was calculated by weighing the collection bag before and after venesection and assuming that 1 mg represented 1 ml of whole blood. All collected autologous blood was stored in the operating room at room temperature. In the control group NVHD was not performed.

On arrival in the operating room, a standardized general anaesthetic technique was used comprising thiopentone 4–6 mg kg^{-1} and fentanyl 5 μg kg^{-1} i.v. for induction and 0.5–1.5% isoflurane (end-tidal) and 70% nitrous oxide in oxygen for maintenance of anaesthesia. Tracheal intubation was facilitated with suxamethonium 1.0 mg kg^{-1} i.v., and surgical relaxation maintained (using a peripheral nerve stimulator) with i.v. pancuronium. After induction of anaesthesia end-tidal carbon dioxide concentration was monitored and the urinary bladder catheterized. Before surgical incision a tourniquet was placed and the operative limb isolated. After placement of the prosthesis, the tourniquet was released and haemostasis performed. Thereafter, the tourniquet was re-inflated until the conclusion of surgery. Intraoperative fluid requirements were administered to maintain heart rate and mean arterial pressure within 20% of baseline values and a urine output of at least 2 ml kg^{-1} h^{-1}. Intraoperative blood loss was assessed by measuring blood volume in suction containers and by weighing all surgical pads and swobs. No blood was administered during operation.

In the post-anaesthesia care unit (PACU) the operative limb was moved using a continuous passive motion device. Autologous blood was reinfused slowly over a 2-h period terminating 2 and 6 h after operation in the NVHD-2 and NVHD-6 groups, respectively. In the control group allogeneic blood was transfused to maintain PCV >28%. On arrival in the PACU and for the duration of hospital admission, subcutaneous heparin 3500 u. was administered three times a day. In the orthopaedic department the decision to transfuse allogeneic blood was taken by an orthopaedic surgeon who was blinded as to the method of treatment. Twenty-four hours after operation the volume of blood in the surgical drain was measured. Thereafter, in order to decrease possible infection, the drain was removed.

Haemoglobin, PCV, prothrombin time (PT), partial thromboplastin time (PTT), platelet count and fibrinogen were measured on arrival in the operating room, after NVHD but before induction, during operation, in the PACU, daily for 9 days and at 3 months after operation. Similarly, serum glucose, sodium, potassium, calcium, urea and creatinine, cholesterol, albumin and bilirubin concentrations were measured at the same times.

Data are expressed as mean (SD or SEM). Descriptive variables were analysed using chi-square tests. Continuous variables were analysed using analysis of variance (with Bonferroni's correction for multiple comparisons). In all cases $P<0.05$ was considered statistically significant.

Results

Patient data (table 1) and duration of anaesthesia and surgery (table 2) were comparable in the three groups. To achieve the target PCV, 1003 (228) and 985 (197) ml of blood were removed over a period of 43 (6) and 41 (4) min in the NVHD-2 and NVHD-6 groups, respectively (table 2). Perioperative crystalloid administration and urine output are presented in table 2. Mean intraoperative surgical blood loss was 370 (78), 353 (63) and 360 (91) ml in the NVHD-2, NVHD-6 and control

Table 1 Patient characteristics for the three groups (mean (SD or range) or number)

	NVHD-2	NVHD-6	Control
n	10	10	10
Age (yr)	71 (61–87)	65 (54–71)	72 (60–82)
Sex (M/F)	2/8	1/9	2/8
Weight (kg)	71 (10)	78 (15)	72 (11)
Height (cm)	155 (5.6)	159 (8.1)	154 (5.7)
ASA (I/II/III)	6/4/0	7/3/0	5/3/2

Table 2 Anaesthetic data (mean (SD))

	NVHD-2	NVHD-6	Control
Venesection (ml)	1003 (228)	985 (197)	
Venesection (min)	43 (6)	41 (4)	
Ringer's lactate (ml)	4310 (633)	4370 (334)	1890 (375)
Blood loss (ml)			
Intraoperative	370 (78)	353 (63)	360 (91)
24-h drain	409 (94)	495 (122)	575 (193)
Urine output (ml)	1775 (103)	1165 (176)	658 (346)
Anaesthesia time (min)	241 (25)	229 (33)	227 (21)
Surgery time (min)	201 (23)	188 (35)	183 (19)

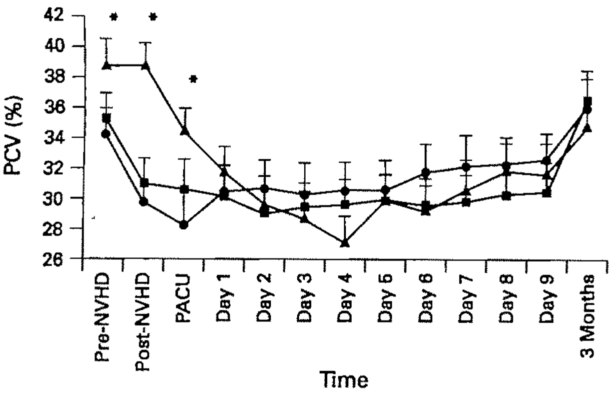

Figure 1 Mean (SEM) perioperative packed cell volume (PCV) in groups NVHD-2 (■), NVHD-6 (●) and in the control group (▲) before and after normovolaemic haemodilution (NVHD), in the post-anaesthesia care unit (PACU) and up to 3 months after operation. *$P<0.05$ compared with groups NVHD-2 and NVHD-6, respectively.

groups, respectively. Twenty-four hours after operation, the volume of blood collected from the surgical drains was 409 (94), 495 (122) and 575 (193) ml in the NVHD-2, NVHD-6 and control groups, respectively.

As a result of the study design, before induction of anaesthesia PCV values in the two NVHD groups were significantly lower than those in the control group. Similarly, on arrival in the PACU a significantly higher PCV was recorded in the control group. During the postoperative period, PCV in the control group decreased, reaching its lowest point on day 4 after operation. However, because of allogeneic blood transfusion, statistical significance was not reached (fig. 1).

In the control group, significantly ($P<0.024$) more allogeneic blood was transfused after operation (table 3). All control patients received allogeneic blood transfusions. A total of 21 u. of packed cells were transfused, with each patient receiving at least 2 u. of blood (table 3). Between days 3 and 6 days after operation, 17 u. of allogeneic blood were transfused. In the NVHD-2 group, six patients received allogeneic blood transfusions and a total of 7 u. of packed cells were administered. Five patients received 1 and one patient received 2 u. of blood. In the NVHD-6 group, five patients received 1 u. of allogeneic blood.

In all patients skin discolouration and swelling caused by subcutaneous haematoma were noted in the ipsilateral dependent thigh and flank.

Preoperative platelet count, PT and PTT were similar in the three groups, and after haemodilution no significant changes were recorded in the NVDH-2 and NVHD-6 groups. Postoperative evaluation of these variables revealed no significant difference between the three groups. Compared with baseline, blood fibrinogen increased significantly in all three groups. While these values remained high until discharge, maximal concentrations were recorded 4 days after operation.

NVDH had no effect on perioperative glucose, calcium, creatinine, urea and electrolytes, cholesterol or bilirubin concentrations. A similar decrease in serum albumin concentration was noted in all groups.

On day 4 after operation, one patient in group NVHD-2 complained of sudden, intense right-sided chest pain which was followed by both circulatory and respiratory arrest. Despite extensive resuscitation the patient died. Because of family preference no post mortem was performed.

Patient follow-up 3 months after operation revealed a PCV of 36.8%, 36.3% and 35.1% in the NVHD-2, NVHD-6 and control groups, respectively. Fibrinogen concentrations measured at this time were similar to preoperative values.

Discussion

The results of this study demonstrated that acute NVHD was an effective blood conservation strategy when performed for total knee replacement. Patients who underwent acute haemodilution required

Table 3 Postoperative allogeneic blood administration in the three treatment groups. n=patient per group. Numbers in table represent number of units administered to patient per postoperative day

	NVDH-2									NVDH-6									Control								
	Postoperative days																										
n	1	2	3	4	5	6	7	8	9	1	2	3	4	5	6	7	8	9	1	2	3	4	5	6	7	8	9
1		2														1					2						
2																								2			
3		1																					2				
4		1																				1	1				
5			1																			2					
6													1									2					
7			1										1													2	
8														1								2					
9			1								1											2					
10																			1	1	1						

significantly less postoperative allogeneic blood. In contrast, between days 3 and 6 after operation, nine patients in the control group received allogeneic blood, most receiving at least 2 u.

Analysis of the postoperative PCV data suggests that NVHD directly influenced transfusion requirements and may have effected postoperative blood loss (fig. 1). As expected from the study design, in the immediate postoperative period PCV in the control group was significantly higher compared with groups NVHD-2 and NVHD-6, respectively. After autologous blood transfusion there was no significant difference in postoperative PCV between the three groups. Therefore, as PCV was stable and the allogeneic transfusion greater in the control group, it appears that NVHD may reduce postoperative blood loss.

As postoperative PCV and allogeneic blood requirements were similar in the NVHD-2 and NVHD-6 groups, it appears that the timing of the autologous blood administration did not effect postoperative allogeneic blood requirements. This may be explained by the relatively short time interval between autologous blood transfusion (2 and 6 h after operation). However, autologous blood was kept at the patient's bedside and stored at room temperature. A longer transfusion time interval between groups would have required more elaborate storage and safety facilities and consequently reduced the attractiveness of NVHD as a blood conservation strategy.

In previous studies the use of acute NVHD has been associated with variable results. In a retrospective analysis of patient records Goodnough and colleagues[16] demonstrated only modest blood conservation after acute preoperative NVHD in patients undergoing radical prostatectomy. Furthermore, during surgical correction of scoliosis, retrospective uncontrolled studies demonstrated that 42–66% of patients who underwent NVHD required postoperative allogeneic blood transfusion.[15 20 21] These studies differ from our investigation in both study design and timing of autologous blood transfusion. In previous investigations prospective studies were not performed and the efficacy of NVHD was determined by comparison with historical controls. Furthermore, as both scoliosis surgery and radical prostatectomy are traumatic procedures associated with significant intraoperative blood loss, autologous blood was transfused either during or on completion of the operative procedure. Thus the potential allogeneic blood transfusion-sparing effects of NVHD may have been lost.

We postulate that the postoperative allogeneic blood-sparing effect demonstrated in this study was likely multifactorial. First, Milam and colleagues[22] suggested that in polycythaemic children undergoing cardiac surgery, NVHD results in improved blood flow in the microcirculation and thus decreases coagulopathies and consequent postoperative bleeding. Second, fresh autologous blood is rich in platelets and clotting factors. This together with improved microcirculation may result in decreased postoperative bleeding.[23–26] It is of interest that in our study perioperative PT, PTT, platelets and fibrinogen concentrations were unaffected by the treatment. However, we measured quantitative rather than qualitative function. Furthermore, NVHD may modify the activity of components of the clotting cascade which were not measured. Third, as NVHD decreases PCV, blood with a low red blood cell mass may have been lost into the extravascular compartment. This is supported by the fact that an ipsilateral thigh and flank haematoma was noted in all patients. As intraoperative and 24-h blood loss were similar in the three groups, we suggest that "diluted" blood formed the haematoma in the two haemodilution groups. However, the time of onset and extent of this haematoma were difficult to compare.

In our opinion the sudden death reported in our study was a consequence of the surgical procedure rather than the anaesthetic technique. As the fatal event occurred 4 days after operation and the patient complained of acute right chest pain before cardiorespiratory collapse, we conclude that a massive pulmonary embolism was the likely cause of the patient's death. This theory is supported by the fact that the incidence of deep vein thrombosis and pulmonary embolism after total knee replacement is 40–84% and 1.7%, respectively.[27–29] Unfortunately, a post mortem was not performed.

This study design may be criticized as the trigger to transfuse after discharge from the PACU was based on the orthopaedic surgeon's "transfusion culture" rather than predefined criteria. It is for this reason that the majority of patients in the two NVHD groups received only 1 u. of allogeneic blood. In our opinion patients who required only 1 u. of allogeneic blood were probably transfused inappropriately. If this subset of patients were excluded from statistical analysis the effect of NVHD on postoperative blood requirements would have been even more significant.

We conclude that the efficacy of acute NVHD is likely to be improved in procedures associated with minimal intraoperative but significant postoperative blood loss. Therefore, for total knee replacement, acute haemodilution is a convenient and effective blood conservation strategy. While the exact mechanism of this blood conservation is unclear, to maximize allogeneic blood conservation strict postoperative transfusion criteria must be defined.

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Ondansetron compared with metoclopramide in the treatment of established postoperative nausea and vomiting[†]

P. Diemunsch, C. Conseiller, N. Clyti, J. P. Mamet and the French Ondansetron Study Group

Summary

We have studied 746 males and females undergoing general anaesthesia for any type of surgical procedure in a double-blind, controlled, randomized study. After experiencing at least one nausea and/or one emetic episode in the 6 h after recovery from anaesthesia, patients received either ondansetron 4 mg i.v. or metoclopramide 10 mg i.v. Patients were observed for postoperative nausea and vomiting (PONV) for 24 h after drug administration. Complete control of PONV was achieved more frequently in the ondansetron-treated patients compared with the metoclopramide-treated patients during the 24-h period (59% *vs* 41% ($P<0.001$) and 44% *vs* 34% ($P=0.006$) for emetic episodes and nausea, respectively). Furthermore, ondansetron was associated with greater patient satisfaction than metoclopramide ($P<0.001$) with 49% and 32% of patients, respectively, very satisfied. The overall incidence of adverse events was similar in the ondansetron (7%) and metoclopramide (8%) groups. Ondansetron was as well tolerated and more effective than metoclopramide for all assessment criteria in the treatment of established PONV. (*Br. J. Anaesth.* 1997; **79**: 322–326).

Key words
Vomiting, antiemetics. Vomiting, nausea. Vomiting, incidence. Vomiting, nausea, surgical factors.

Postoperative nausea and vomiting (PONV) is a troublesome phenomenon after general anaesthesia. PONV is also a major concern for patients undergoing outpatient surgery under general anaesthesia and may complicate and delay discharge from hospital.[1] In some cases, for example ophthalmic surgery, PONV can compromise surgery.[2]

Ondansetron has been shown to be effective and well tolerated in the prevention and treatment of PONV.[3 4] For prevention, it seems logical to use ondansetron for some procedures known to be associated most commonly with PONV.

In the treatment of established PONV, therapeutic practices differ from one country to another and agents such as metoclopramide and droperidol are often administered. Droperidol has been demonstrated to be effective at low doses but its haemodynamic and sedative effects limit its use, particularly when rapid awakening is sought.[5] Metoclopramide is also used widely as an antiemetic. It was for these reasons that we compared ondansetron with metoclopramide.

In the treatment of established PONV, Claybon[4] compared i.v. ondansetron 1, 4 or 8 mg with placebo in 2812 male and female patients in three different studies. The combined results showed that ondansetron 4 mg was the optimal dose for treating established PONV.

In this study we have compared, under routine clinical conditions, the efficacy and safety of ondansetron 4 mg i.v. with metoclopramide 10 mg i.v. in the treatment of established PONV in patients receiving general anaesthesia.

Patients and methods

This randomised, double-blind, parallel-group comparative study was carried out in 60 French centres. The study was approved by the local Ethics Committee and written informed consent was obtained from each patient.

We studied male and female inpatients, aged 18–75 yr, having undergone surgery under general anaesthesia and scheduled to be hospitalized for at least 30 h after recovery. The main exclusion criteria were patients who had received an antiemetic drug in the 24 h before anaesthesia and during the study, patients who experienced nausea, vomiting, or both, in the 24 h before anaesthesia, and patients who were scheduled to have a nasogastric tube *in situ* after operation. A balanced general anaesthetic technique was used for all patients and the use of propofol was permitted only for induction of anaesthesia.

The following concurrent medications were defined for the purpose of the study: premedication with any benzodiazepine, if required; induction of anaesthesia with i.v. agents such as thiopentone,

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P. Diemunsch, md, Hôpital Civil, 67091 Strasbourg Cedex, France. C. Conseiller, md, Hôpital Cochin, 75014 Paris Cedex, France. N. Clyti, phd, J. P Mamet, phd, Laboratoire Glaxo Wellcome, 75016 Paris Cedex, France. Accepted for publication: April 22, 1997.

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propofol; analgesia with any i.v. opioid, as required; maintenance of anaesthesia with inhaled nitrous oxide in oxygen and supplemented with halothane, enflurane or isoflurane, as required; neuromuscular block and antagonism with any agent, as required; and postoperative analgesia with opioid or non-opioid analgesics, or combinations of the two, administered parenterally, rectally or orally.

Other concurrent medications (e.g. antibiotics) administered to the patient during the study were also recorded.

Patients who experienced one episode of nausea (duration at least 5 min) or one emetic episode (defined as a single vomit or retch or any number of continuous vomits separated by at least 1 min), or both, during the 6 h after recovery from anaesthesia were allocated randomly to receive either ondansetron 4 mg i.v. or metoclopramide 10 mg i.v. as a slow i.v. injection administered over at least 5 min in a double-blind study (the study drug was administered by a third person, nurse or anaesthetist, who did not participate in the study).

Rescue antiemetic medication was given to patients in case of severe nausea, if an emetic episode occurred at least 15 min after drug administration or at any time at the patient's request. Any licensed antiemetic could be used as rescue medication.

ASSESSMENTS

The number of recurrent emetic episodes during the 15 min to 24 h after the end of drug administration and the time to the first emetic recurrent episode were recorded. The highest nausea grade using a four-point scale (none, mild, moderate, severe) was recorded during the same period. Global satisfaction with the study medication experienced by the patient was assessed using a five-point scale, 24 h after the end of drug administration, as very satisfied, quite satisfied, neither satisfied nor unsatisfied, rather unsatisfied or very unsatisfied. The safety of the study drug was assessed by monitoring adverse events throughout the 24-h period. The investigators recorded any unexpected adverse events, irrespective of their potential relation to the study drug.

All concomitant treatments were recorded over the same period.

STATISTICAL ANALYSIS

The study sample size (n=768) was based on the assumption that complete control of emetic episodes at 24 h would be achieved in 50% of patients in the ondansetron group and in 40% of patients in the metoclopramide group, using a two-sided test with a significance level of 5% and a power of 80%. Nine hundred patients were planned to be included in order to take into account non-evaluable patients. The number of patients took into account the fact that an interim analysis of the primary end-point was planned on the first 450 patients included in the study. Statistical analysis was performed on the intent-to-treat population, that is all patients who were randomized and received medication.

The primary end-point was the proportion of patients experiencing no emetic episode (no retches and/or no vomits) and without rescue or withdrawal during the 15 min to 24 h after drug administration. Patients who were rescued or withdrawn from the study were considered to be treatment failures from that time onwards. Comparisons were made between the two treatment groups using the chi-square test.

Secondary end-points were the number of recurrent emetic episodes, time to first recurrent emetic episode, emesis by gender, incidence and severity of nausea, global satisfaction of the patient, percentage of patients who were rescued, and incidence and severity of adverse events.

Time to first recurrent emetic episode was compared between the two groups using the log-rank test, and associated curves were obtained according to the Kaplan–Meier method. Statistical tests used were either the Wilcoxon rank sum test for the number of emetic episodes, severity of nausea and rescue medication, or the Mantel–Haenszel test for patient global satisfaction. Incidence of nausea was assessed by the two-sided chi-square test.

Patients who received rescue antiemetic medication were regarded as treatment failures. Patients experiencing more than five emetic episodes or who were rescued or withdrawn were assigned the value of five episodes for the purpose of analysis. In addition, rescued patients were assigned a severe nausea grade (data adjusted for rescue).

Results

INTERIM ANALYSIS

Interim analysis of the primary end-point was performed on the first 450 patients (235 ondansetron-treated patients and 215 metoclopramide-treated patients).

Results of the interim analysis showed that the percentage of patients with no emetic episodes and who were not rescued or withdrawn from the study between 15 min and 24 h after drug administration was significantly higher in the ondansetron group than in the metoclopramide group (60% *vs* 42%; P<0.001). It was therefore decided to terminate recruitment into the study at this point and perform the final analysis on all recruited patients. By the time these results were obtained the total number of recruited patients was 746.

FINAL ANALYSIS

A total of 2032 patients who gave written informed consent were screened; 746 of these experienced one episode of nausea or emetic episode, or both, and were allocated randomly to receive ondansetron 4 mg i.v. (n=380) or metoclopramide 10 mg i.v. (n=366). Patient characteristics (table 1), type of surgery performed (table 2), medical conditions and concurrent treatments were well matched in the two groups. However, there was a large proportion of women (91%). The main types of operations performed were gynaecological (52%) and gastro-intestinal (12%). Also, duration of anaesthesia and

Table 1 Patient characteristics (mean (SD or range) or number (%))

	Ondansetron group	Metoclopramide group	Total
No. of randomized patients	380	366	746
Sex (No. (%))			
Male	34 (9)	30 (8)	64 (9)
Female	346 (91)	336 (92)	682 (91)
Age (yr)	44 (18–22)	45 (19–74)	45 (18–82)
Weight (kg)	63 (12)	63 (11)	63 (11)

Table 2 Type of surgery performed

	Ondansetron group (n=380)	Metoclopramide group (n=366)	Total
Gynaecological	50%	54%	52%
Gastrointestinal	13%	12%	12%
ENT	10%	10%	10%
Breast	7%	6%	7%
Orthopaedic	6%	6%	6%
Thyroid	6%	7%	6%
Thoracic and cardiovascular	4%	1%	3%
Other	4%	4%	4%

Table 3 Duration of anaesthesia and time to recovery from anaesthesia

	Ondansetron group	Metoclopramide group
Duration of anaesthesia (min)		
Mean	116	121
SD	61	67
Median	105	110
Range	13–375	10–510
Time to recovery from anaesthesia (min)		
Mean	26	25
SD	23	22
Median	20	20
Range	0–230	0–225

time to recovery from anaesthesia were similar in the two groups (table 3).

A similar proportion of patients in both groups received opioid analgesics (176 in the ondansetron group, 159 in the metoclopramide group), non-opioid analgesics (150 in the ondansetron group, 152 in the metoclopramide group) or no analgesics (54 in the ondansetron group, 55 in the metoclopramide group).

Other prognostic factors for emesis were well matched in the two groups, that is previous history of PONV (150 patients in the ondansetron group and 147 in the metoclopramide group), previous history of motion sickness (61 patients in the ondansetron group and 65 in the metoclopramide group), use of propofol (172 patients in the ondansetron group and 168 in the metoclopramide group) and use of atropine (22 patients in the ondansetron group and 26 in the metoclopramide group).

PRIMARY END-POINT

Table 4 Number of emetic episodes recorded between 15 min and 24 h after administration of the study drug. Significance level based on Wilcoxon rank sum test: $P<0.001$

No.of emetic episodes	Ondansetron group (n=380) (No. (%))	Metoclopramide group (n=366) (No. (%))
0	223 (59)	151 (41)
1	34 (9)	32 (9)
2	13 (3)	18 (5)
3	5 (1)	12 (3)
4	4 (1)	6 (2)
≥5	1 (<1)	3 (<1)
Rescued or withdrawn because of treatment failure	100 (26)	144 (39)

The percentage of patients with no emetic episode and who were not rescued or withdrawn from the study between 15 min and 24 h after the end of drug administration was significantly higher in the ondansetron group (59%; 223 of 380) than in the metoclopramide group (41%; 151 of 366) ($P<0.001$; chi-square test).

SECONDARY END-POINTS

Number of emetic episodes

The number of emetic episodes in the ondansetron group was significantly smaller than that in the metoclopramide group ($P<0.001$) (table 4).

Time to first emetic episode

Analysis of the median time to the first emetic episode showed that patients in the ondansetron group remained free of emesis for longer than patients in the metoclopramide group ($P<0.001$) (fig. 1). The median time to the first emetic episode was 5 h in the metoclopramide group compared with more than 24 h in the ondansetron group (59% of ondansetron treated-patients were still free of emesis at 24 h).

Incidence and severity of nausea

The percentage of patients with no nausea adjusted

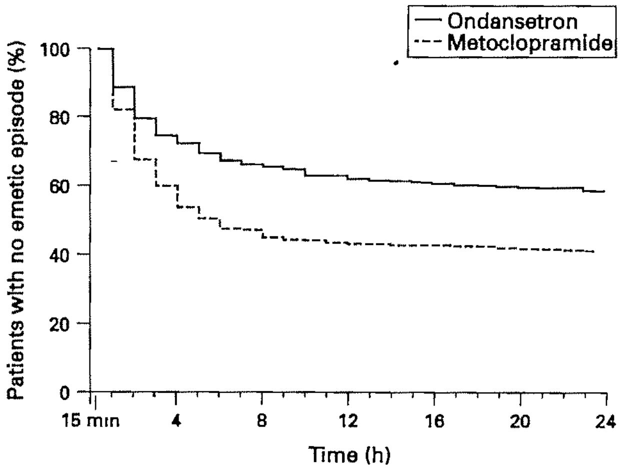

Figure 1 Time to first emetic episode for the period from 15 min to 24 h after drug administration in the ondansetron (n=380) and metoclopramide (n=366) groups.

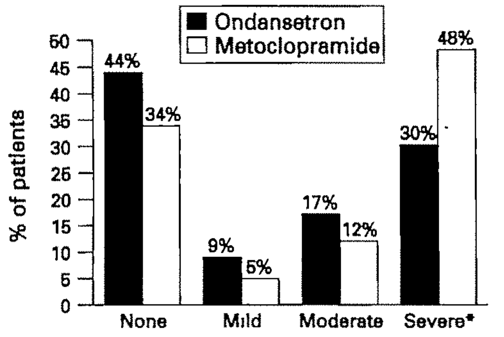

Figure 2 Worst grade of nausea recorded between 15 min and 24 h after drug administration in the ondansetron (n=380) and metoclopramide (n=366) groups. Wilcoxon rank sum test comparing the distribution of nausea grade: P<0.001. (*Rescued patients were assigned a severe nausea grade.)

for rescue between 15 min and 24 h after drug administration was significantly higher in the ondansetron group than in the metoclopramide group (44% *vs* 34%; P=0.006).

Distribution of the worst nausea grade adjusted for rescue between 15 min and 24 h after drug administration was significantly lower in the ondansetron group (P<0.001) (fig. 2).

Global satisfaction of the patient

Distribution of patient global satisfaction was significantly different between the two groups (P<0.001). There were more very satisfied patients in the ondansetron group than in the metoclopramide group (49% *vs* 32%) (fig. 3).

Rescue medication

More patients received rescue medication in the metoclopramide group than in the ondansetron group (39% *vs* 26%; P<0.001).

Safety

A similar proportion of patients experienced adverse events in both treatment groups (ondansetron 7%, metoclopramide 8%). The majority of adverse events were assessed as non-drug-related; 1% of patients in the ondansetron group and 2% of patients in the metoclopramide group experienced a drug-related adverse event. The most frequently reported adverse event was headache, which was assessed as drug-related in four patients (one in the ondansetron group, three in the metoclopramide group). Six patients experienced a serious adverse event during the study; none was assessed as related to study medication.

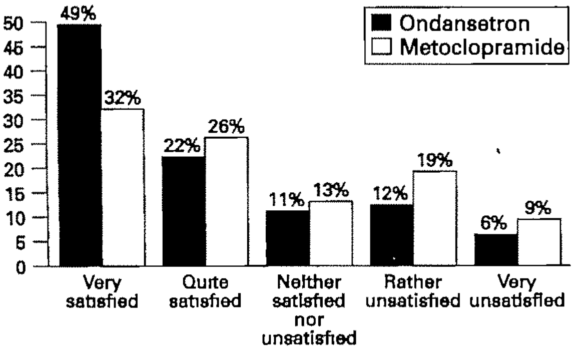

Figure 3 Patient global satisfaction in the ondansetron (n=380) and metoclopramide (n=366) groups. Mantel–Haenszel test comparing the distribution of global satisfaction: P<0.001.

A total of four patients withdrew because of adverse events, none being related to the study treatment.

Discussion

PONV is a common postoperative problem with an overall incidence of approximately 25%.[6] The type of surgery influences the occurrence of PONV: gynaecological surgery is associated with the highest incidence of PONV[7–9] followed by abdominal surgery.[10] Our study population was in accordance with this incidence (746 patients experienced PONV from a total of 2032 patients screened).

A combined analysis of two different studies published by Claybon[4] showed that a single i.v. dose of ondansetron 4 mg was superior to placebo for complete control of emetic episodes (45% *vs* 21%) and complete control of nausea (38% *vs* 20%). Moreover, results of these studies showed that a higher dose of ondansetron (8 mg) had no additional benefit in term of efficacy:safety ratio.

The results of our study showed that ondansetron was significantly superior to metoclopramide for the control of recurrent emetic episodes (59% *vs* 41%; P<0.001) and for the control of nausea (44% *vs* 34%; P=0.006). The median time to the first emetic episode after drug administration was greater than 24 h in the ondansetron group compared with 5 h in the metoclopramide group (P<0.001). Moreover, severity of nausea was less important in the ondansetron group than in the metoclopramide group (P<0.001). Finally, our study evaluated patient global satisfaction which had not previously been routinely investigated in PONV: patients in the ondansetron group reported higher satisfaction scores than those in the metoclopramide group (P<0.001).

Comparative studies in the prevention of PONV showed that ondansetron was superior to metoclopramide[11 12] and droperidol,[13 14] or both.[15 16] Moreover, the reduced requirement for further rescue antiemetics[13 17] may suggest that ondansetron provides greater benefit. Ondansetron has further advantages compared with droperidol: it is not associated with extrapyramidal effects and sedation.[18] Metoclopramide is also known to induce extrapyramidal side effects, especially when used for chemotherapy-induced emesis.[19]

In the treatment of established PONV, there are some data comparing ondansetron with other antiemetics.[4 20 21] These three studies showed that there was no significant difference between ondansetron and droperidol. However, the results could be criticized because of the small study population. In addition, evaluation of patients was followed for only a short period of time after treatment.

To date, this is the largest study comparing ondansetron with an active comparator in the treatment of established PONV. Our results showed that ondansetron was more effective than metoclopramide. The incidence of adverse events was low and similar in both the ondansetron and metoclopramide groups. The majority of adverse events were assessed as non-drug-related. In addition, the nature of adverse events was consistent with previous experience.[3 5 11]

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Histological support for the difference between malignant hyperthermia susceptible (MHS), equivocal (MHE) and negative (MHN) muscle biopsies

P. MEZIN, J.-F. PAYEN, J.-L. BOSSON, E. BRAMBILLA AND P. STIEGLITZ

Summary

The aim of this study was to find, using modern techniques, any histological differences in muscle biopsies between malignant hyperthermia (MH) susceptible (MHS), MH equivocal (MHE) and MH negative (MHN) patients. On the basis of the European MH contracture test carried out in 83 patients, 23 were shown to be MHS, nine MHE and 51 MHN. Four lesions were found with a significantly high frequency in MHS and MHE biopsies: muscle fibre hypertrophy and atrophy, internal nuclei and myofibrillar necrosis. These four lesions were observed together in 35% of MHS but in none of the MHE or MHN biopsies. Three of these lesions occurred together in 57% of MHS, 33% of MHE and 4% of MHN biopsies. Our results support a histological difference between MHE, MHS and MHN biopsies and attempt to contribute towards a better definition of MHE status. (*Br. J. Anaesth.* 1997; **79**: 327–331).

Key words
Malignant hyperthermia. Measurement techniques, histology.

Cases of malignant hyperthermia (MH) have been reported since 1960[1] but it was only in 1978 that the first pathological observations on series of muscles from MH susceptible (MHS) patients were described.[2 3]

Studies generally report only a small number of cases; there are few recent data, and histological lesions in MH equivocal (MHE) patients have never been described in comparison with those in MHS patients. Our study included photonic and ultrastructural examination, morphometrical analysis, examining possible immunoglobulin deposits with the use of anti-dystrophin antibodies (in some cases) and statistical analysis.

Patients and methods

The 83 patients studied included 43 females and 40 males of more than 16 yr of age. All patients came from families either found to be or suspected of being sensitive to MH because of an anaesthetic incident. Of the 83 patients, 18 were probands. Their biopsies were performed at least 6 months after the anaesthesic episode. Mean age was 35.3 (range 16–67) yr.

MH SENSITIVITY TEST

Patients underwent biopsy of the vastus medialis muscle under a femoral nerve block with 1% lignocaine injection. The muscle strips were subjected to halothane and caffeine contracture tests. The classification criteria used to differentiate between MHS, MHE and MH negative (MHN) were those of the European protocol.[4]

METHODS

Part of the biopsy was reserved for pathological examination which, for the 83 patients, was carried out by the same pathologist.

The usual colourations and histoenzymatic reactions carried out routinely for diagnosis were performed on the semi-fine sections of frozen material.[5] These allow appreciation of the appearance of the muscle fibres in addition to myofibrillar and mitochondrial functioning.

The search for possible immunoglobulin deposits was carried out under fluorescent light after application of immune serum to IgA, IgG, IgM, C3 and fibrinogen. Anti-dystrophin sera (DYS1, DYS2 and DYS3) were applied to the muscles of MHS patients in which atrophied fibres and necrosis were observed. The presence of dystrophin was revealed by a peroxydase–anti-peroxydase reaction. Ultrafine sections were used for ultrastructural examination after muscle inclusion in epon.

Finally, morphometrical analysis was carried out with the aid of a Biocom image analyser.[6] Type I and II muscle fibres were differentiated by a reaction showing myofibrillar ATPase. Mean diameters were measured using the general histological program Histo 200.

P. MEZIN, PHD, E. BRAMBILLA, MD (Laboratoire de Pathologie Cellulaire); J.-F. PAYEN, MD, PHD, P. STIEGLITZ, MD (Département d'Anesthésie-Réanimation); J.-L. BOSSON, MD, PHD (Service d'Informatique et d'Imagerie Médicale (SIIM)); Hôpital Albert Michallon, 38043 Grenoble cedex 09, France.
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STATISTICAL ANALYSIS

A chi-square test was used to establish if the frequency variations of the lesions in the MHS, MHE and MHN muscles were significant. This analysis was completed by a test of linearity designed to evaluate the prevalence of MHS and MHE using the number of lesions observed. The risk of first species ($P=0.05$) was used with the Bonferroni correction for the multiple tests. The relative risks are given within a confidence interval of 0.05 calculated according to the Miettinen formula. The Spierman correlation test was used for studying the relation between contracture strength and either the age of the patient or number of lesions.

Results

PHOTONIC MICROSCOPY EXAMINATION

The most commonly encountered lesions in the muscles of MHS patients under photonic microscopy examination were hypertrophy and atrophy of muscle fibres, internal nuclei and myofibrillar necrosis (fig. 1). The frequency of each lesion was significantly higher in MHS than in MHE and MHN muscles (fig. 2A). The frequency of hypertrophic fibres in the MHE group was significantly different from that in the MHS or MHN group ($P=0.05$). For atrophic fibres, internal nuclei and necrosis, the MHE group was not significantly different from the other two.

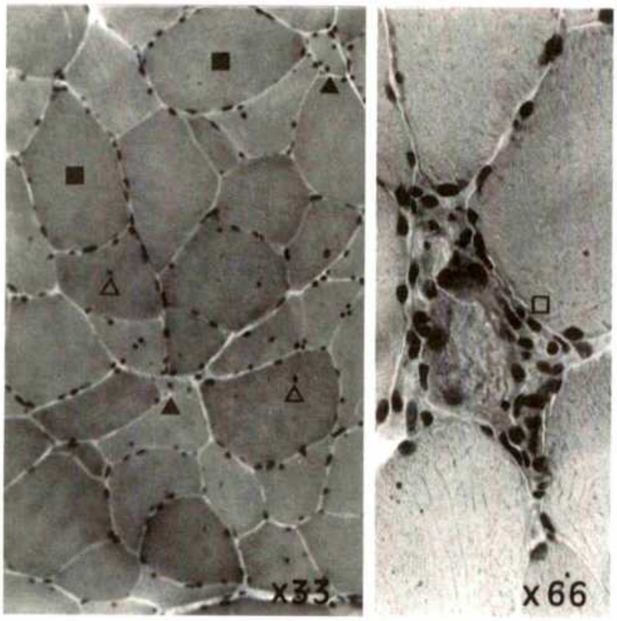

Figure 1 Histological examination. ■=Hypertrophic fibres, ▲=atrophic fibres, △=internal nuclei and □=necrosis.

The four lesions were present in 35% of MHS cases (eight of 23) but did not occur together in MHE or MHN patients ($P<0.0001$). Of the four lesions, three were found together in 57% of MHS cases (13 of 23), in 23% of MHE cases (three of nine) and in 3% (two of 51) of MHN cases ($P<0.001$) (fig. 2B). The test of linearity for empirical frequencies showed that the risk of being MHS was nil if the muscle had either no or only one of these lesions. This risk was multiplied by three if two of these lesions were present, and was multiplied by nine if there were three or four lesions.

The other lesions observed under light microscopy were cores and/or myofibrillary disorganization, segmentation and inflammatory infiltrates. The cores were isolated lesions and were observed either alone or with micro-disruption of the Z material. There were no significant differences in the frequency of these lesions between the three groups.

CONTRACTURE TEST

The force of contracture for 2% halothane was graded from I to V as: 0.2 g<CF<0.3 g=I, 0.3 g<CF<0.5 g=II, 0.5 g<CF<1 g=III, 1 g<CF<2 g=IV, 2 g<CF=V. There was a positive correlation between the force of contraction and the number of lesions (correlation coefficient=0.4) ($P=0.04$).

ANTI-DYSTROPHIN ANTIBODIES

In all MHS cases, muscle fibres showed a regular marking of normal intensity along the sarcolemma membrane.

MORPHOMETRIC ANALYSIS

For each group of patients, mean diameter was calculated for both men and women and for type I and type II fibres. Mean diameters were always

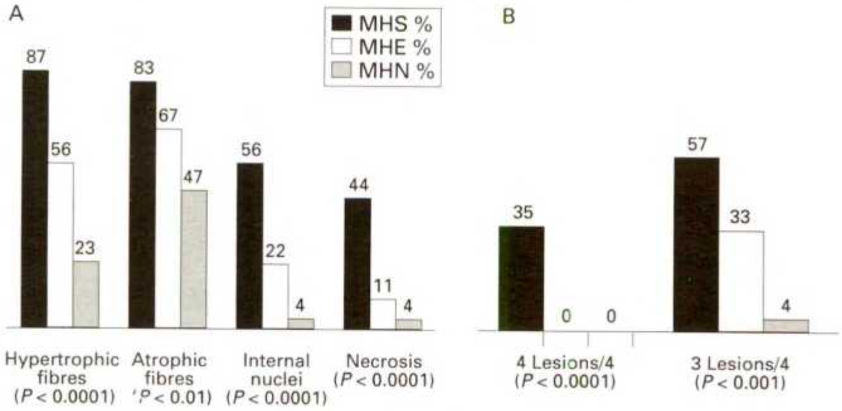

Figure 2 A: Principal lesions observed under light microscopy in the three groups of patients. B: Association of these lesions. %=Number of patients with the lesion/total number of patients.

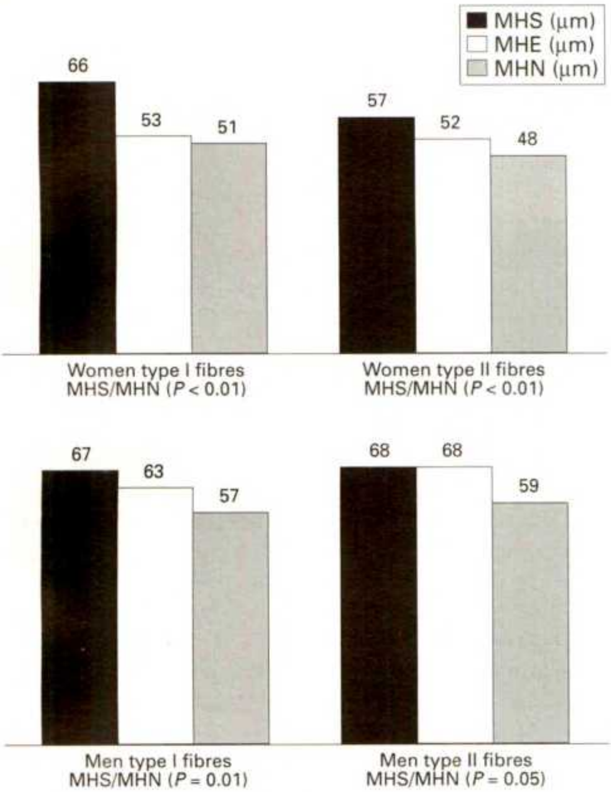

Figure 3 Morphometrical analysis: muscle fibre mean diameters in men and women in the three groups of patients.

higher in MHS than those in MHE or MHN patients (fig. 3).

In MHE, mean diameters of type I and type II fibres were not significantly different from those in MHS and MHN. Conversely, for the two types of fibres and for men and women, mean diameters in MHS were always significantly different from those in MHN.

EXAMINATION UNDER FLUORESCENT LIGHT

Intravascular C3 deposits, linked in one case to IgM deposits, were observed in three MHS patients. Fibrinogen deposits were present in one MHE patient. Four MHN patients had intravascular C3 deposits, which were associated with IgM deposits in two cases. In a fifth MHN patient, only IgM deposits were present. Apparently these deposits were not associated with MH pathology. Their presence was linked to other pathologies specific to the patients and are therefore not discussed.

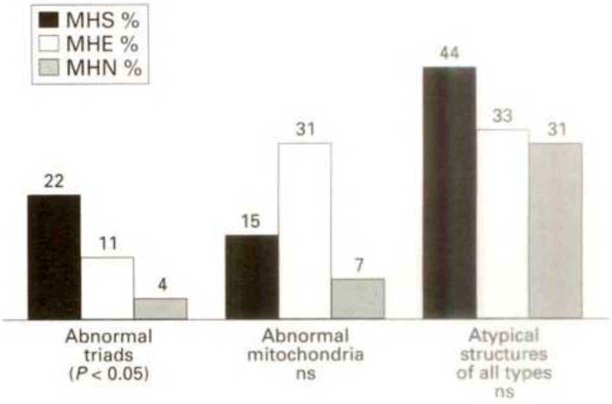

Figure 5 Principal lesions observed under ultrastructural examination in the three groups of patients.

ULTRASTRUCTURAL EXAMINATION

Micro-disruptions of the Z material, invisible under light microscopy, were observed, as were various atypical structures in the muscle fibres. Most frequently, these consisted of L ampula dilatations in triads, but also sarcoplasmic vesicle accumulations, tubular aggregates, spiralated formations and atypical mitochondria (fig. 4). Their frequency is reported in figure 5.

Although relatively uncommon, only the presence of abnormal triads was significantly different in the three groups ($P=0.05$). More precisely, the MHS group was significantly different from the MHN group ($P=0.01$), but the MHE group was not significantly different from the other two.

Finally, the muscle was considered totally free of lesions and atypical structures in 9% of MHS (two of

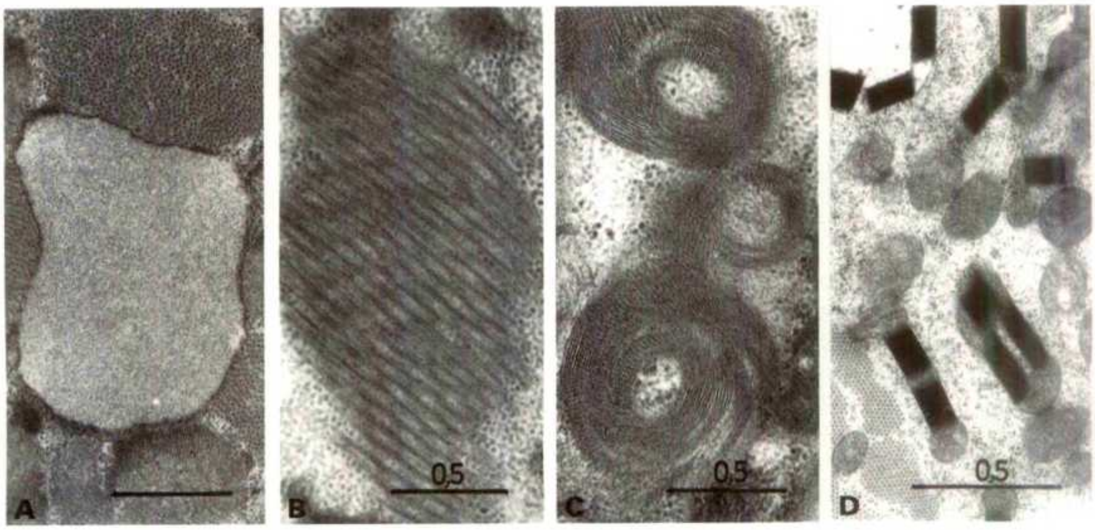

Figure 4 Ultrastructural examination: some sarcoplasmic atypical inclusions. A: L ampula dilatation in a triad; B: tubular aggregate; C: concentric laminated bodies; and D: crystalloid inclusions in mitochondria.

23), 22% of MHE (two of nine) and 29% of MHN (15 of 51) muscles (ns).

Discussion

Among the 83 patients tested for susceptibility to MH, 23 (28%) had a positive reaction, nine (11%) an equivocal reaction and 51 (61%) were negative. For the MHE population, our results resembled those of Figarella and Pellissier[7] (6%) and those of Krivosic and colleagues[8] (17%).

MH has often been linked to muscular pathologies, the most frequent being central core disease.[9–12] MHS cases have been observed in patients suffering from Duchenne muscular dystrophy,[13] limb girdle dystrophy,[10] glycogen storage disease,[9] congenital myotony,[14] McArdle disease,[15] myotonic dystrophy,[16] congenital muscular dystrophy[17] and mitochondrial myopathy.[18] MHS has also been reported in association with neuropathic diseases (spinal atrophy or neuropathy[19]) or with various pathologies such as diabetus mellitus[9] or sudden death of the newborn.[10]

The 83 patients in our study were clinically healthy and histological examination did not reveal any specific pathology. In particular, no patient had a mitochondrial myopathy, apparent as ragged red fibres and negative fibres with cytochrome oxydase reaction, as reported by Figarella and Pellissier.[7] Conversely, in common with Isaacs,[3] we observed under photonic or electronic microscopy, abnormal mitochondria in 15% of MHS, 31% of MHE and 7% of MHN biopsies. However, the lesions were disseminated in muscle fibres, were not numerous and were therefore not significant.

The lesions observed most frequently under light microscopy were hypertrophy and atrophy of muscular fibres, internal nuclei and myofibrillar necrosis; some have been described by Harriman and colleagues[2] and by Isaacs[3] since 1978. The most frequent lesion was hypertrophic fibres, found in 87% of MHS and 56% of MHE cases. Curiously, Harriman did not report this lesion in 1987[20] and observed it rarely in 1988 [21] but his study was only qualitative. The hypertrophy we observed was confirmed by morphometric analysis. Mean diameters of muscle fibres were higher in MHS than in MHE or MHN patients, taking into account fibre type and patient sex. This observation confirms those of Harden-Mayor and colleagues,[22] Bergeson and colleagues[23] and Krivosic and colleagues[8] who, in common with us, observed no abnormalities in the distribution of the two fibre types.

These authors agreed on the observation of atrophic fibres. Ellis[24] also described them as the only morphometric abnormality. We observed atrophic fibres much more frequently in muscles of MHS and MHE patients than in MHN patients. They were angular in a large number of cases but their disseminated arrangement and absence of grouping by fibre type does not support an association with a neurogenic pathology.[19]

Internal nuclei were much more numerous in MHS (56% of cases) than in MHE (22%) or MHN (4%) biopsies. Harden-Mayor and colleagues[22] observed them in 49% of MHS cases and Harriman and colleagues[2] in more than 25% of fibres of MHS subjects. Conversely, Rieske-Nielsen[16] described an increase in the total number of nuclei and Figarella and Pellissier[7] observed no difference. This disparity may be a result of the great variety of anomalies that can be observed from one patient to another or from one family to another.

Lesions of necrosis or myophagy, or both, were far more numerous in MHS (44%) than in MHE (11%) and MHN (4%) biopsies. Necrosis, linked to the presence of atrophic and hypertrophic fibres, prompted us to apply anti-dystrophin antibodies in an attempt to detect Duchenne or Becker muscular dystrophy. We found regular marking of muscular fibres in all cases and therefore abandoned this diagnostic hypothesis.

Depending on the lesion studied, the MHE group either is or is not significantly different from the MHS group or from the MHN group.

The combined presence of the four lesions (hypertrophy, atrophy, internal nuclei and necrosis) is particularly interesting. This was observed in 35% of MHS subjects but not in MHE or MHN subjects. Moreover, three of the four lesions were found together in 57% of MHS, in 33% of MHE and in only 4% of MHN biopsies. Only one other study[8] reported a link between morphometrical and morphological lesions; these authors found 1.8 alterations per case in the group of MHS and MHE patients, and only 0.5 alterations per case in the MHN group.

Statistical analysis showed that the concomitant presence of these four lesions was not a result of chance and that there were significant differences between the three groups. As the number of associations of these abnormalities increased, so did the risk that a patient was MHE or MHS. On the other hand, we observed no significant relation between the age of the patients and the presence of 1–4 lesions in their biopsies. However, in the MNH population, the atrophic fibres were slightly more numerous in older patients. Moreover, we observed no difference in the number of lesions in MH probands, non-MH probands and other patients, or in the number of lesions and the severity of the MH episode in these patients. However, the number of these lesions was correlated to contracture strength in the *in vitro* contracture test.

Under ultrastructural examination we observed atypical structures in muscle fibres, more numerous in MHS than in MHE or MHN. Particular attention was paid to examination of atypical triads, showing dilatations of the sarcoplasmic reticulum cisternae. They were more numerous in MHS (22%) than in MHE (11%) or MHN (4%). Only one author,[16] reported the presence of abnormal triads in three of 10 probands. The rarity of this observation is surely because ultrastructural studies are rare and, when they are carried out, only take into account a small number of patients. Yet, the number of cases in which we observed abnormal triads was low considering the fact that MH crisis is probably linked to an anomaly in the release of calcium at the triad site.

Finally, we considered the muscle to be totally free of lesions in 9% of MHS, 22% of MHE and 29% of MHN cases. These results were statistically significant but very different from those of Harriman[20] who found normal muscle in 70% of MHS subjects. However, our results are closer to those of Figarella and Pellissier[7] (26%) and Stathousers[25] (23%) but these authors did not carry out morphometrical analysis and, despite having studied a large number of cases, ultrastructural examination was performed only in exceptional cases.

In summary, the lesions we observed most frequently in MHS and MHE muscle biopsies were hypertrophy, atrophy, necrosis of fibres and internal nuclei. Their combined occurrence allowed us to distinguish significantly between the muscles of MHS, MHE and MHN patients.

In general and taking all lesions into account, we observed a linear effect for their increase in the three categories of patients: MHN, MHE and MHS. The equivocal group was situated between the two others and was either significantly different or not depending on the lesions concerned.

A correlation was observed between the histopathological appearance of the muscles and their reactivity to the contracture test and, if morphological observation alone does not make it possible to diagnose susceptibility or an equivocal reaction to MH, it does provide a good probability index.

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Detection of a novel mutation at amino acid position 614 in the ryanodine receptor in malignant hyperthermia

K. A. QUANE, H. ORDING, K. E. KEATING, B. M. MANNING, R. HEINE, D. BENDIXEN, K. BERG, R. KRIVOSIC-HORBER, F. LEHMANN-HORN, T. FAGERLUND AND T. V. MCCARTHY

Summary

Malignant hyperthermia (MH) is a potentially fatal autosomal dominant disorder of skeletal muscle and is triggered in susceptible people by all commonly used inhalation anaesthetics and depolarizing neuromuscular blocking agents. To date, eight mutations in the skeletal muscle ryanodine receptor gene (RYR1) have been identified in malignant hyperthermia susceptible (MHS) and central core disease (CCD) cases. We have screened the RYR1 gene in affected individuals for novel MHS mutations by single stranded conformational polymorphism (SSCP) analysis and have identified a G to T transition mutation which results in the replacement of a conserved arginine (Arg) at position 614 with a leucine (Leu). The Arg614Leu mutation was present in three unrelated MHS individuals of 151 investigated. The mutation was not detected in 148 normal chromosomes and segregated precisely with MHS in family members from one of the probands where DNA was available for analysis. This mutation occurs at the same position as the previously identified Arg to Cys mutation reported in all cases of porcine MH and in approximately 5% of human MH. A comparison of the phenotypes of the Arg614Leu and Arg614Cys probands is presented. (*Br. J. Anaesth.* 1997; **79**: 332–337).

Key words
Malignant hyperthermia. Genetic factors, hyperthermia. Receptors, ryanodine.

Malignant hyperthermia (MH) is a clinically heterogeneous autosomal dominant disorder elicited in susceptible individuals by widely used volatile anaesthetics and depolarizing neuromuscular blocking agents and characterised by skeletal muscle hypermetabolism.[1 2] The reported incidence of MH ranges from approximately 1 per 10 000 to 1 per 50 000 anaesthetics with an apparently higher incidence in children.[3]

MH also occurs in pigs and is closely associated with muscle hypertrophy. Biochemical studies on porcine MH indicate that the primary defect in MH susceptible (MHS) cases is in the skeletal muscle calcium release channel, commonly termed the ryanodine receptor (RYR1).[4] Sequence analysis of the porcine RYR1 gene has shown that a point mutation is present in MH pigs that results in an arginine (Arg) to cysteine (Cys) substitution at position 615 (Arg615Cys).[5] A mutation equivalent to the pig Arg615Cys has also been found in human MH.[6] The human mutation is known as the Arg614Cys mutation and results from a C1840T transition mutation.

In addition to this mutation, another seven RYR1 point mutations have been identified in MHS and central core disease (CCD)[7] pedigrees, namely Arg163Cys,[8] Gly248Arg,[9] Gly341Arg,[10] Ile403Met,[8] Tyr522Ser,[11] Gly2433Arg[12 13] and Arg2434His.[14] Collectively, these mutations have been found in approximately 10% of Caucasian MHS cases. Identification of these mutations firmly establishes the RYR1 gene as a susceptibility gene in MH and indicates that mutations are likely to be present in the RYR1 gene in all RYR1 linked families.

In an effort to identify new mutations in the RYR1 gene causing MH we have undertaken systematic screening of the 15 099 bp coding sequence of the RYR1 gene in unrelated MHS individuals for mutations. We describe the identification of a novel Arg614Leu mutation which we detected in a MHS pedigree and two unrelated MH probands.

KATHLEEN A. QUANE, MB, PHD, KATHERINE E. KEATING PHD, BERNADETTE M. MANNING, BSC, TOMMIE V. MCCARTHY, PHD, Department of Biochemistry, University College, Cork, Ireland. HELLE ORDING MD, DMSC, DIANA BENDIXEN, MD, Herlev Hospital, University of Copenhagen, Herlev Ringvej 75, DK 2730, Herlev, Denmark. ROLAND HEINE, PHD, FRANK LEHMANN-HORN, MD, Department of Applied Physiology, University of Ulm, Albert Einstein Allee 11, D-89069 Ulm, Federal Republic of Germany. KARE BERG, MD, PHD, TORE FAGERLUND, MD, Department of Anaesthesia, Ulleval University Hospital, Kirkeveien 166, N-0407 Oslo, Norway. RENEE KRIVOSIC-HORBER, MD, Malignant Hyperthermia Unit, Hospital B, CHRU de Lille 59037, Lille Cedex, France. Accepted for publication: April 10, 1997.

Correspondence to T. V. McC.

Patients and methods

Screening for single nucleotide changes in the RYR1 gene of MHS patients requires amplification of the entire gene from each individual in short segments and subsequent investigation of each of these gene segments for nucleotide changes. The RYR1 gene spans 158 kb of genomic DNA and contains more than 100 exons.[15] For amplification purposes, we chose to use RYR1 complementary DNA (cDNA) as muscle biopsy material was available from MHS individuals. For synthesis of cDNA, total RNA was first extracted by guanidinium thiocyanate[16] from the muscle tissue and first strand cDNA synthesis was performed as described previously.[10] PCR primers were designed using the computer programme OLIGO version 4.0,[17] so that the entire 15 099 bp coding sequence of the RYR1 gene[18] could be amplified in short (200–450 bp) overlapping segments, using cDNA as template in the amplification reaction (the sequence of the 64 PCR primer pairs and PCR conditions are available on request).

Screening for single nucleotide changes in RYR1 segments amplified by PCR from the MHS patients was performed using the well established single stranded conformation polymorphism (SSCP) method[19] under three different electrophoretic conditions, as described previously.[10] The DNA bands on the polyacrylamide gel were detected by autoradiography. Normal samples were included in the SSCP analysis as controls to allow identification of normal alleles.

Sequence analysis of PCR amplified fragments exhibiting aberrant SSCP patterns was performed as described previously.[10]

For segregation studies, genomic DNA was extracted from peripheral blood as described previously.[20] A 74-bp fragment spanning the G1841T mutation of the RYR1 gene was amplified from genomic DNA using PCR, as described previously.[6] For SSCP detection, the samples were run on a 6% polyacrylamide gel (acrylamide N, N'methylenebisacrylamide=99:1) with 5% glycerol at room temperature for 1.5 h. The G1841T SSCP was detected by autoradiography.

For the investigations reported here, muscle samples were obtained from 29 MHS patients and five MH negative (MHN) individuals through the Lille, Copenhagen and Ulm MH testing centres. Patients were tested for MH susceptibility using the standardized European Malignant Hyperthermia Group IVCT procedure.[21]

Results

SSCP ANALYSIS OF THE RYR1 GENE IN MH

SSCP polyacrylamide gel band patterns, which did not correspond to those observed in normal individuals, were detected in eight areas of the RYR1 gene in patient 12F. Seven of these were considered to be polymorphisms (normal variations in the DNA sequence which do not result in an abnormal protein product[9 14]) as they were present in some of the control samples (normal individuals) and/or were found to be silent mutations after DNA sequence analysis. However, direct sequencing of the RYR1 segment 1727–1993 in patient 12F, which also demonstrated an aberrant SSCP pattern, revealed the presence of the single base substitution G1841T which results in the replacement of an Arg with a Leu at position 614 (fig. 1).

The presence of the G1841T missense mutation in genomic DNA extracted from blood samples was verified by checking the appropriate amplified products for the presence of the SSCP banding pattern characteristic of the presence of the mutation and by direct sequencing.

To establish if the Arg614Leu mutation was present in the normal population, 148 normal chromosomes were examined for the presence of the mutation. None displayed the candidate mutation. In order to determine if these mutations were present in the RYR1 gene of other MHS pedigrees or CCD pedigrees, 122 additional

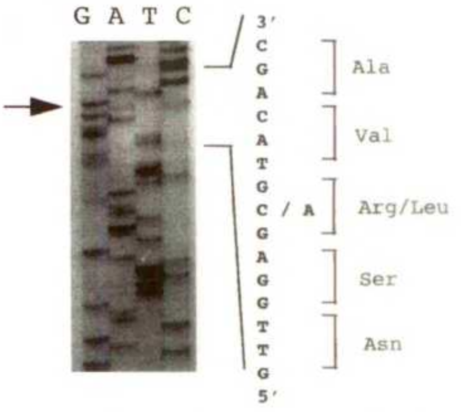

Figure 1 Nucleotide sequence of the mutated region in RYR1 1727–1993 segment from patient 12F. Sequencing was carried out using alpha-32P dCTP and was performed with the reverse primer 1993 so that the sequence of the reverse strand was obtained. The position of the C1841A transition on the reverse strand sequence (G1841T on the forward strand) is indicated by the arrow.

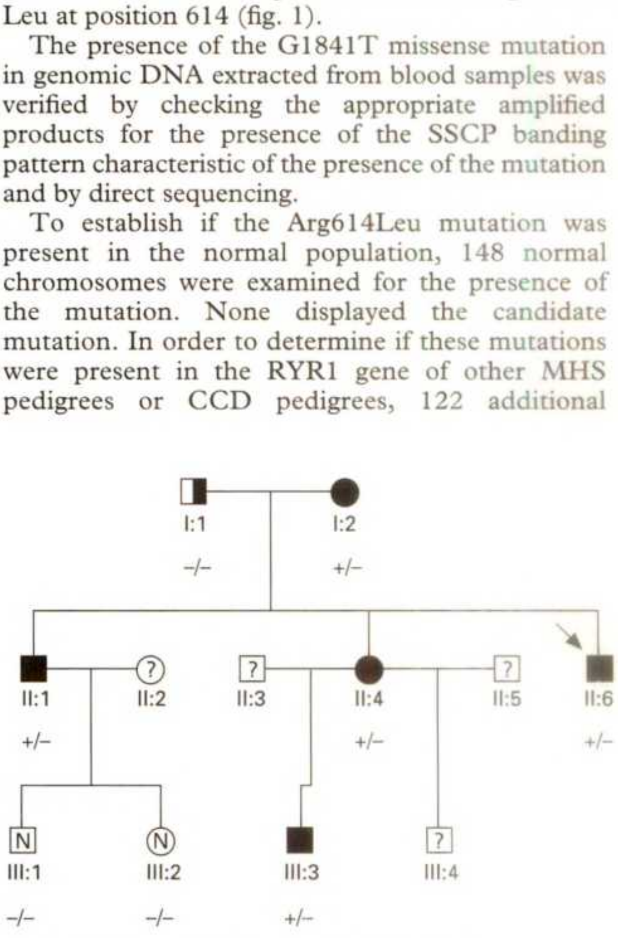

Figure 2 Pedigree of MH proband D15. Symbols: black=MHS; open=MHN; half-black=MHE(h); open with question mark=disease status unknown. The proband (individual II-6) is indicated by an arrow. Segregation of the Arg614Leu RYR1 mutation is also indicated: + =presence of the mutant allele; − =presence of the normal allele.

Table 1 Results of the *in vitro* contracture test in (A) individuals with the Arg614Leu mutation, including members of pedigree D15 and (B) probands with the Arg614Cys mutation. The halothane and caffeine thresholds are the concentrations of halothane (%) and caffeine (mmol litre^{-1}), respectively, at which a contracture of 0.2 g tension is generated. *Taken from.[22] NA=not available

	Family	ID	Diagnosis	Halothane threshold (%)	Contracture at 2% halothane (g)	Caffeine threshold (mmol litre^{-1})	Contracture at 2 mmol litre^{-1} caffeine (g)	RYR1 mutation
A	D15	I-1	MHE(h)	2.0	0.4	3.0	0	Arg614Leu absent
		I-2	MHS	0.5	3.2	0.5	2.1	Arg614Leu present
		II-1	MHS	0.5	2.5	0.5	1.85	Arg614Leu present
		II-4	MHS	0.5	4.15	1.0	2.3	Arg614Leu present
		II-6 (Proband)	MHS	0.5	1.8	1.0	1.0	Arg614Leu present
		III-1	MHN	>3.0	0	4.0	0	Arg614Leu absent
		III-2	MHN	>3.0	0	4.0	0	Arg614Leu absent
		III-3	MHS	0.5	1.4	0.5	1.7	Arg614Leu present
	1GR	Proband	MHS	0.5	Fibres disrupted	0.5	1.0	Arg614Leu present
	12F	Proband	MHS	0.5	1.5	1.5	0.58	Arg614Leu present
B	G2	Proband	MHS	1.0	0.2	1.5	0.8	Arg614Cys present
	G3	Proband	MHS	2.0	0.5	2.0	0.2	Arg614Cys present
	G7	Proband	MHS	0.5	Fibres disrupted	0.5	0.64	Arg614Cys present
	10F	Proband	MHS	NA	0.9	NA	0.23	Arg614Cys present
	8F	Proband	MHS	0.5	NA	NA	0.25	Arg614Cys present
	1F	Proband	MHS	2.0	0.2	1.0	0.3	Arg614Cys present
	MH011*	302	MHS	1.0	ND	2.0	0.2	Arg614Cys present
	MH011*	408	MHS	0.5	0.5	0.5	ND	Arg614Cys present
	MH011*	503	MHS	1.0	0.9	2.0	0.8	Arg614Cys present
	MH011*	501	MHS	0.5	2.5	1.5	1.3	Arg614Cys present
	MH011*	506	MHN	>3.0	0.0	>4.0	0.0	Arg614Cys present

Table 2 Clinical indicators (abnormal signs and laboratory findings) recorded during MH reactions and used to determine the MH raw score in the case of three unrelated Arg614Leu probands (R614L) and nine unrelated Arg614Cys probands (R614C).[23] ND=not determined

Individual	Anaesthetic administered	Suxamethonium administered	Process I: Rigidity	Process II: Muscle breakdown	Process III: Respiratory acidosis	Process IV: Temperature increase	Process V: Cardiac involvement	Other indicators	Raw score
GR1 (R614L)	Halothane	Yes	0	15	0	0	3	ND	18
12F (R614L)	Thiopentone Isoflurane	No	0	15	15	15	3	5	53
D15 (R614L)	Thiopentone Halothane	Yes	15	10	10	15	3	ND	53
G2 (R614C)	Halothane	Yes	15	5	0	0	3	5	28
G3 (R614C)	Isoflurane	Yes	15	15	15	15	3	25	88
G4 (R614C)	Halothane	Yes	15	15	ND	15	3	5	53
G5 (R614C)	Halothane	Yes	15	15	ND	0	ND	ND	30
G6 (R614C)	Enflurane	Yes	ND	ND	15	10	3	25	53
G7 (R614C)	Halothane	Yes	0	ND	ND	10	0	25	35
1F (R614C)	Halothane	No	15	15	ND	0	3	ND	33
8F (R614C)	Halothane	No	15	15	15	15	3	5	68
10F (R614C)	Halothane	No	ND	ND	ND	15	3	ND	18

unrelated MHS and five unrelated CCD patients were investigated for the presence of these mutations. The mutation was detected in one Danish (D15) and one German (GR1) MHS patient.

The family of individual D15 (fig. 2) was investigated to determine if the Arg614Leu mutation co-segregated with the MHS phenotype. The mutation co-segregated with the MHS phenotype in this family (fig. 2). The families of individuals 12F and GR1 were unavailable for analysis.

Interestingly, Arg614 is the position of the original porcine RYR1 mutation (Arg615Cys and Arg614Cys in pigs and humans, respectively) which accounts for all cases of porcine MH investigated to date and for approximately 5% of human MH cases.[6] As Arg614 is the position of two MH causative mutations, it is of interest to compare the contracture data and clinical phenotypes. Table 1 presents the IVCT results of individuals carrying the Arg614Leu mutation (pedigree of D15, 1GR, 12F) and results of individuals carrying the Arg614Cys mutation, including six MH probands and five individuals from pedigree MH011 described by Deufel and colleagues.[22] Individual 408 of the MH011 pedigree is homozygous for the Arg614Cys mutation although the two C1840T base transitions segregate independently. Individual 506 who is heterozygous for the Arg614Cys mutation was diagnosed MHN by the IVCT and is the only reported MHN individual carrying the Arg614Cys mutation.[22]

The contracture thresholds (the concentration of caffeine or halothane at which a contracture of 0.2 g tension is generated) of the three probands with the Arg614Leu mutation varied significantly for caffeine (0.5–1.5 mmol litre^{-1}) whereas the halothane threshold was the same in all three cases (0.5%)

(table 1). Individual 506 of pedigree MH011, who is MHN and heterozygous for the Arg614Cys mutation, registered a caffeine threshold >4.0 mmol litre^{-1} and a halothane threshold >3.0%. The contracture thresholds of MHS individuals with the Arg614Cys mutation ranged from 0.5 to 2.0 mmol litre^{-1} for caffeine and from <0.5% to 2.0% for halothane.

In an effort to compare the clinical phenotype of MHS individuals with the Arg614Cys and Arg614Leu mutations, we applied the MH clinical grading scale devised by Larach and colleagues[23] (table 2). In this system, the quantitative likelihood that an adverse anaesthetic event represents MH is based on points assigned to specific abnormal signs and laboratory findings (clinical indicators) observed during an acute anaesthetic reaction. Points are assigned for each indicator present. As several agreed upon indicators are the manifestations of the same process, only the single indicator with the highest score within a given process would count towards the raw score. These points are then summed to produce a raw score that an adverse anaesthetic reaction is a MH event.

Discussion

In an ongoing effort to identify new mutations in the RYR1 gene causing MHS, we have investigated the RYR1 gene in unrelated MHS patients for the presence of new mutations. Analysis of the RYR1 cDNA sequence was performed in preference to analysis of the genomic DNA sequence (>100 exons) as only 64 PCR primer pairs are required for the former while more than 100 primer pairs are required for the latter.[15] Furthermore, as muscle biopsy samples from MHS individuals are readily available after the IVCT, availability of RNA for cDNA synthesis is not a limiting factor. The RYR1 PCR primers described here work reproducibly to give good quality PCR products suitable for SSCP analysis and DNA sequencing.

In this study, we detected a novel Arg614Leu mutation in three of 151 unrelated Caucasian MHS probands. The pedigree of one of these probands was available for analysis and the Arg614Leu mutation segregated with MHS in this pedigree (fig. 2). Individual I-1 of this pedigree, diagnosed as MHE(h) by the IVCT, was negative for the presence of the mutation. Examination of the contracture records showed that this individual exhibited a significant response to halothane (0.4 g at 2% halothane). The observation that some patients can produce significant responses in the IVCT in the absence of the reported segregating mutation has been reported previously by us in families where the Gly341Arg and Gly2433Arg mutations segregated with MHS.[10 12]

The Arg614Leu mutation was not detected in 148 normal chromosomes. Furthermore, examination of the RYR1 genes sequenced to date[5 17] and related isoforms[24–27] indicate that Arg614 is a functionally important amino acid in the RYR proteins as it is conserved across species (fig. 3). Therefore, the Arg614Leu mutation is not likely to be a coincidental polymorphism and is likely to cause MHS in patients bearing the mutation.

The Arg614Cys and Arg614Leu mutations are the result of a C1840T and G1841T transition, respectively, at a CpG dinucleotide in the RYR1 gene sequence. Methylation of a CpG dinucleotide to 5-methyl cytosine creates a mutation hot spot because of the high frequency of deamination of 5-methyl cytosine to thymidine, resulting in the TpG dinucleotide and the complementary dinucleotide CpA.[28] CpG dinucleotides are the site of approximately 35% of all known disease causing point mutations and of these, more than 90% are accounted for by C to T or G to A transitions.[29] In contrast, the Arg614Leu mutation is the result of a G1841T transition at this CpG dinucleotide.

As Arg614 is the position of two mutations potentially causative of MH, we compared the contracture data and clinical phenotypes of probands (tables 1 and 2). Comparison of the caffeine and halothane contracture thresholds (the concentrations at which a contracture of 0.2 g tension is generated) of individuals carrying the Arg614Leu and Arg614Cys mutations (table 1) suggests that the Arg614Leu mutation exhibits a more severe phenotype in the IVCT.

Mutations in the RYR1 gene that cause MH are thought to make the Ca^{2+} release channel sensitive to lower concentrations of agonists.[30] This hypersensitive gating of the channel enhances rates of Ca^{2+} release from the sarcoplasmic reticulum during anaesthesia which results in sustained muscle contraction and sustained glycolytic and aerobic metabolism associated with MH.[30] The suggestion of a more potent effect of the Arg614Leu mutation compared with the Arg614Cys mutation in the IVCT could be explained by increased sensitivity of the RYR1 protein with the Arg614Leu mutation to

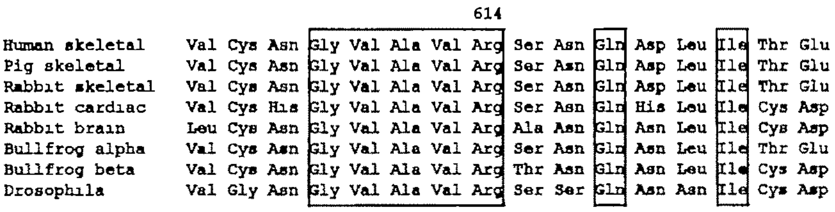
614
Human skeletal Val Cys Asn Gly Val Ala Val Arg Ser Asn Gln Asp Leu Ile Thr Glu
Pig skeletal Val Cys Asn Gly Val Ala Val Arg Ser Asn Gln Asp Leu Ile Thr Glu
Rabbit skeletal Val Cys Asn Gly Val Ala Val Arg Ser Asn Gln Asp Leu Ile Thr Glu
Rabbit cardiac Val Cys His Gly Val Ala Val Arg Ser Asn Gln His Leu Ile Cys Asp
Rabbit brain Leu Cys Asn Gly Val Ala Val Arg Ala Asn Gln Asn Leu Ile Cys Asp
Bullfrog alpha Val Cys Asn Gly Val Ala Val Arg Ser Asn Gln Asn Leu Ile Thr Glu
Bullfrog beta Val Cys Asn Gly Val Ala Val Arg Thr Asn Gln Asn Leu Ile Cys Asp
Drosophila Val Gly Asn Gly Val Ala Val Arg Ser Ser Gln Asn Asn Ile Cys Asp

Figure 3 Amino acid sequence of the regions of the RYR1 protein and related isoforms flanking the residue Arg614.[5 18 24–27] Residues identical to the human are boxed. Ala=Alanine, Arg=arginine, Asn=asparagine, Asp=aspartic acid, Cys=cystine, Gln=glutamine, Glu=glutamic acid, Gly=glycine, His=histidine, Ile=isoleucine, Leu=leucine, Ser=serine, Thr=threonine and Val=valine.

stimulators of channel opening such as halothane and caffeine. However, the sample number of this study was small and a larger sample size is necessary to verify this observation.

The clinical details of MHS probands carrying the Arg614Leu and Arg614Cys mutations are presented in table 2. The MH clinical grading scale devised by Larach and colleagues[23] was applied to each individual. As all the clinical indicators (clinical signs and laboratory tests) were not recorded or performed in each case during the anaesthetic reaction, direct comparison of the MH raw scores of probands was not possible (table 2). In addition, early diagnosis of an MH episode followed by prompt treatment implies that many of the clinical signs of an MH episode do not occur and a low raw score would thus result. This severely restricts the usefulness of the clinical grading scale for phenotype–genotype correlation studies. As seen in table 2, the phenotype of both the Arg614Leu and Arg614Cys mutations is variable: the presence of several clinical signs of the MH episode, such as muscular rigidity, respiratory acidosis, temperature increase.

Detection of the Arg614Leu mutation brings to nine the total number of RYR1 mutations reported to date in MHS/CCD pedigrees. These mutations cluster in two regions of the protein: seven mutations in the amino terminal region (residues Arg163 to Arg614) and two mutations near the centre of the protein (Gly2433 and Arg2434). Arg614 is the first amino acid of the RYR1 protein where two potentially causative mutations for MH are described.

Acknowledgements

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Since submission of this manuscript, two additional mutations in the RYR1 gene have been reported in MH.[31 32]

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British Journal of Anaesthesia 1997; 79: 338–341

Changes in inflammatory mediators during orthotopic liver transplantation

M. C. BELLAMY, H. F. GALLEY AND N. R. WEBSTER

Summary

Transplantation is associated with an inflammatory rejection response. Graft reperfusion causes typical haemodynamic and biochemical responses. In this study we have investigated the relationship between these haemodynamic responses and changes in circulating inflammatory mediators after graft reperfusion in 10 consecutive patients undergoing orthotopic liver transplantation. After reperfusion, systemic vascular resistance index decreased (P=0.011) and cardiac index increased (P=0.038). These characteristic haemodynamic changes of the reperfusion syndrome were accompanied by global increases in cytokine concentrations. Plasma concentrations of leukotrienes decreased, while thromboxane B_2 and platelet activating factor remained increased throughout. Reperfusion-mediated changes in inflammatory mediators may account for the haemodynamic disturbance. (*Br. J. Anaesth.* 1997; **79**: 338–341).

Key Words
Liver, transplantation. Polypeptides, cytokines. Immune response.

Liver transplantation is associated with a complex sequence of events, including immune activation, haemodynamic derangement and long-term immune rejection reactions. Reperfusion injury, thought to be a result of increased oxygen derived free radical release and characterized by loss of endothelial cell viability, occurs after cold ischaemic storage and subsequent reperfusion.[1–4] Deranged endothelial cell function may in turn result in leucocyte activation and release of inflammatory mediators which may then cause graft damage and rejection. While preservation injury of the graft may result from activation of Kupffer cells and consequent local injury,[5] our study was concerned with the host systemic response to graft reperfusion.

Extra-hepatic effects of hepatic reperfusion result in haemodynamic deterioration and biochemical responses similar to those seen in sepsis. The causes of this response are poorly defined; animal models of ischaemia–reperfusion syndrome have demonstrated increased expression of tumour necrosis factor-α (TNFα).[6] In these models, TNFα and haemodynamic changes resemble those seen in sepsis, where release of TNFα and a range of interleukins (IL) are associated with reduction in systemic vascular resistance and an increased cardiac index.[7] Moreover, cytokines are involved in rejection reactions which are a complication of liver transplantation.[8 9] Thus ischaemia–reperfusion syndrome is likely to have several important intra- and extra-hepatic effects on outcome. The mechanisms underlying reperfusion syndrome have not been elucidated. We have therefore examined changes in cytokines and arachidonic acid metabolites after reperfusion to investigate the relationship between inflammatory and haemodynamic responses.

Patients and methods

Approval for the study was obtained from the local Clinical Research (Ethics) Committee. We studied 10 consecutive adult patients undergoing elective orthotopic liver transplantation after obtaining written informed consent.

Peripheral venous and radial artery cannulae were inserted and anaesthesia was induced with alfentanil 0.1 mg kg^{-1} and midazolam 0.1 mg kg^{-1}. Neuromuscular block was facilitated by a bolus dose of atracurium 0.5 mg kg^{-1} followed by an infusion of 0.4 mg $kg^{-1} h^{-1}$. After tracheal intubation, the lungs were ventilated to normocapnia with oxygen-enriched air and 1 MAC of isoflurane. Anaesthesia was supplemented with an infusion of alfentanil 0.1 mg $kg^{-1} h^{-1}$. A central venous cannula, pulmonary artery catheter and 18-F percutaneous cardiac bypass catheter were inserted according to our usual practice.[10] Dopamine was infused throughout the procedure at a rate of 3 μg $kg^{-1} min^{-1}$. All patients were established on veno-venous bypass at the beginning of the anhepatic phase, at a flow rate of 0.4×cardiac output to help maintain haemodynamic stability.[11] Tranexamic acid 1 g was administered prophylactically, followed by an infusion of 300 mg h^{-1} until the end of surgery.[12] After excision of the liver and before reimplantation, prednisolone 10 mg kg^{-1} was administered. Where necessary, adrenaline was given in incremental boluses of 50 μg to maintain haemodynamic stability at reperfusion.

Serum potassium concentration was maintained

MARK C. BELLAMY, MA, FRCA, Intensive Care Unit, St James's University Hospital, Leeds LS9 7TF. HELEN F. GALLEY, PHD, FIMLS, NIGEL R. WEBSTER, PHD, FRCA, Academic Unit of Anaesthesia and Intensive Care, Institute of Medical Sciences, University of Aberdeen, Aberdeen. Accepted for publication: April 24, 1997.

Correspondence to M. C. B.

Table 1 Changes in inflammatory mediators following graft reperfusion. Data are median (range) and were compared using Wilcoxon signed rank test

	Time III_{-5} (pg ml^{-1})	Time III_{60} (pg ml^{-1})	*P*
Tumour necrosis factor-α	4.4 (4.4–12)	32 (14–154)	0.008
Tumour necrosis factor receptor 1	3033 (2437–5621)	8108 (5783–21940)	0.008
Interleukin-1β	1.0 (1.0–1.3)	1.5 (1.0–15.0)	0.04
Interleukin-1 receptor antagonist	1324 (220–10010)	5467 (653–24660)	0.06
Interleukin-6	376 (82–2855)	2137 (272–24660)	0.02
Interleukin-8	121 (50–338)	743 (398–1575)	0 04
Platelet activating factor	978 (741–2577)	1096 (453–1853)	ns
Thromboxane B_2	330 (120–620)	370 (120–900)	ns
Leukotriene C_4, D_4, E_4	800 (110–6800)	580 (40–1200)	ns

in the range 4.0–5.0 mmol litre^{-1} and ionized calcium in the range 0.8–1.4 mmol litre^{-1}. Blood and colloid (modified fluid gelatin) were infused at 37 °C via a rapid infusion system to maintain the packed cell volume at 0.26–0.32 and central venous pressure at 6–12 mm Hg.

Cardiac output was measured by the triplicate thermodilution method, and cardiac index and systemic vascular resistance index (SVRI) were calculated 5 min before (III_{-5}), and 5, 10, 20, 30 and 60 min (III_5, III_{10}, III_{20}, III_{30} and III_{60}) after graft reperfusion. Blood samples (5 ml) were collected at III_{-5} and III_{60} into plain tubes for assay of cytokines, and into EDTA tubes containing 30 μl of indomethacin 0.04 mol litre^{-1} for measurement of leukotriene and thromboxane. These were centrifuged immediately and stored at −70 °C until assay. Samples were obtained at the same times for assay of platelet activating factor (PAF) and were treated as follows: 2 ml of blood were added immediately to 6 ml of ice-cold methanol and vortex mixed. After centrifugation at 3000 *g* for 20 min, the supernatant was frozen at −70 °C until assay. Enzyme-linked immunoassay was used to measure TNFα, IL-1β, IL-6 and IL-8. Thromboxane B_2, total leukotrienes (LTC_4, D_4 and E_4), TNF receptor 1, IL-1 receptor antagonist (IL-1ra) and PAF were measured using radioimmunoassay. Samples from single patients were assayed in the same batch, and all assays were carried out within 1 month.

STATISTICAL METHODS

Data are expressed as median (range). Changes in cardiac index and SVRI with time were analysed using Friedman analysis of variance. Friedman is a non-parametric approach based on rank. We chose this approach because our numbers were small, and to protect against potential effects of individual "rogue" values. The difference between pre- and post-reperfusion biochemical data was examined using Wilcoxon signed rank test. All statistical tests were performed using SPSS for Windows (v 6.0). Changes were taken to be statistically significant when $P<0.05$.

Results

One patient died during operation, and data from nine patients (five women, median age 49 (range 39–62) yr) are therefore presented. Their diagnoses were primary sclerosing cholangitis (three patients), chronic rejection after previous transplantation (two),

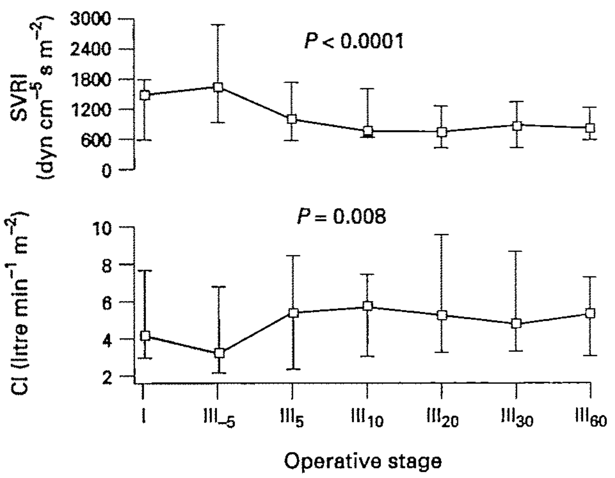

Figure 1 Time course of haemodynamic changes (systemic vascular resistance index (SVRI) and cardiac index (CI)) during orthotopic liver transplantation in nine subjects. Results are shown as median (range) and were analysed using Friedman two-way analysis of variance.

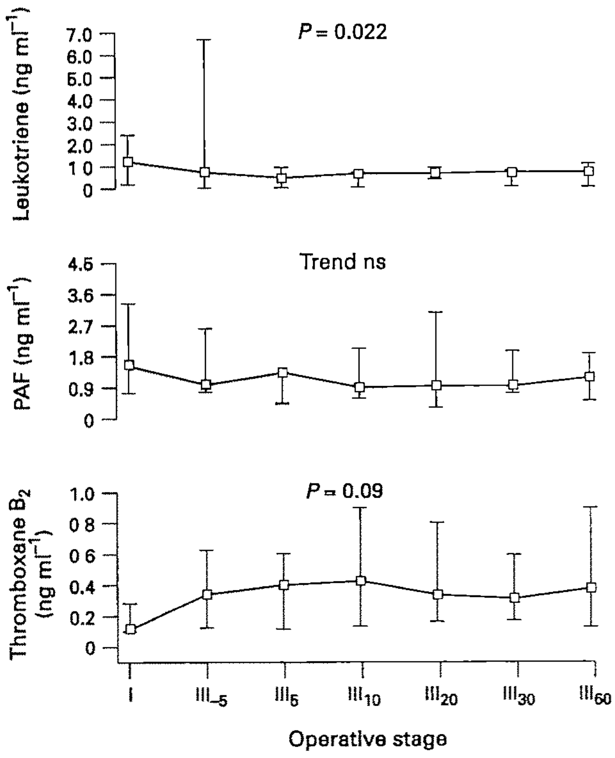

Figure 2 Time course of inflammatory mediator changes during orthotopic liver transplantation in nine subjects. Results are shown as median (range) and were analysed using Friedman two-way analysis of variance.

chronic active hepatitis, sero-negative viral hepatitis, alcoholic cirrhosis and haemochromatosis (one each).

There were significant changes in both cardiac index (P=0.008) and SVRI (P<0.0001) (Friedman) during transplant (fig. 1). Cardiac index increased from 3.3 (2.2–6.8) litre min^{-1} m^{-2} at III_{-5} to 5.4 (2.3–8.4) litre min^{-1} m^{-2} at III_5 (P=0.038, Wilcoxon). SVRI decreased on reperfusion of the liver graft from 1647 (930–2871) dyn s^{-1} cm^{-5} m^{-2} to 883 (561–1727) dyn s^{-1} cm^{-5} m^{-2} (P=0.011).

Concentrations of all cytokines and IL-1ra and TNF receptor 1 increased at III_{60} compared with III_{-5} (table 1). Total leukotriene concentrations showed a decreasing trend with time (fig. 2). The increased leukotriene concentrations seen at III_5 related to a single outlying value. Thromboxane B_2 and PAF concentrations, although increased, remained constant (table 1).

Discussion

We have confirmed a well-defined change in cardiovascular status after graft reperfusion during orthotopic liver transplantation, consisting of marked reduction in systemic vascular resistance and an increase in cardiac output. We have also demonstrated significant changes in circulating concentrations of mediators of inflammation, including cytokines and eicosanoids, after reperfusion.

The endothelium produces several substances which regulate inflammation, including cytokines and arachidonic acid metabolites. Orchestration of the inflammatory response depends on communication between cells by cytokines which regulate the severity and duration of the inflammatory response.

In this study we found increases in TNFα, IL-1β, IL-6 and IL-8 1 h after reperfusion. This contrasts with models of endotoxin-induced sepsis, where increases in TNF concentration in the circulation usually preceded increases in IL-6 and IL-8 by several hours.[13] A previous study also found early intraoperative increases in IL-6.[14] A possible explanation in our patients could be cytokine activation as a result of veno-venous bypass. Cardiopulmonary bypass can trigger an early increase in IL-6 and neutrophil activity.[15 16] Another possibility could be "priming" by high circulating concentrations of PAF seen in this study.

Cytokines produce a biological effect which is receptor mediated. Specific cytokine receptor expression is itself cytokine dependent. Additionally, the interaction between cytokine and receptor may be modulated by the effects of free (circulating) receptor molecules or by circulating antagonists to cellular receptors. The biological action of IL-1β for example is regulated by its receptor antagonist (IL-1ra) and regulated independently by other cytokines as part of the inflammatory process. In addition to increased cytokine concentrations, predictable concomitant increases in IL-1ra and TNF receptor 1 (TNF-R1, a circulating TNF receptor possibly antagonizing the interaction between TNF and its cellular receptor) were found in our study after reperfusion.

Under conditions of ischaemia and reperfusion, oxygen-derived free radicals are produced by activation of xanthine oxidase. We have shown previously increased oxidant stress after graft reperfusion during liver transplantation, associated with haemodynamic changes.[4 17] In this study we have demonstrated elevation of thromboxane B_2 and total leukotrienes in varying proportions in different patients. Oxygen-derived free radicals mediate production of both thromboxanes and leukotrienes.[6] These vasoactive compounds with oxygen derived free radicals act as chemoattractants for leucocytes. Moreover, eicosanoids have been implicated in the increases in intracellular calcium in the leucocyte which trigger cytokine expression.

Lipid mediators of inflammation include PAF and arachidonic acid metabolites. PAF primes macrophages to other inflammatory mediators and alters microvascular permeability. Although PAF did not increase as a result of reperfusion, concentrations were increased compared with previous findings in healthy subjects.[18] Arachidonic acid metabolites, including leukotrienes and thromboxanes, have profound inflammatory and vascular actions and may regulate, and be regulated by, cytokines.

We have shown that in patients undergoing liver transplantation there was an inflammatory response associated with expression of several pro-inflammatory cytokines subsequent to reperfusion in humans. This was accompanied by activation of lipoxygenase and cyclo-oxygenase pathways suggesting ongoing inflammatory activation and endothelial damage. These changes occurred in association with dramatic characteristic haemodynamic changes of the reperfusion syndrome. These changes in cytokines, biochemistry and haemodynamic state resemble those seen in the sepsis syndrome, although unlike septic shock they are precisely predictable. Other workers have shown an association between increases in intraoperative TNFα and IL-6 concentrations with subsequent graft rejection and infection.[14] An understanding of the biochemical and inflammatory processes surrounding graft reperfusion may therefore lead to strategies to improve outcome. We have not considered in this study the role of anti-inflammatory cytokines and further work is required.

Acknowledgements

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Environmental monitoring during gaseous induction with sevoflurane

J. E. HALL, K. A. HENDERSON, T. A. OLDHAM, S. PUGH AND M. HARMER

Summary

Recent research has shown that gaseous induction in adults with sevoflurane is an acceptable technique. This study was undertaken to assess if gaseous induction using sevoflurane carried in both oxygen alone, and in nitrous oxide and oxygen combined, would provide acceptable pollution levels. As an occupational exposure standard has not been set for sevoflurane, we used the target level of 20 ppm set by the manufacturer. Environmental monitoring was carried out in the anaesthetic room during eight lists where consecutive triple vital capacity sevoflurane inductions were performed. Time-weighted averages for both gases over the duration of the lists were well below the occupational exposure standards (mean 1.1 (range 0.6–1.7) for sevoflurane and 17.3 (12–23) for nitrous oxide). There were high peak concentrations during the induction process (8.3 (4.1–17) for sevoflurane and 172.4 (65–310) for nitrous oxide) although these decreased to low concentrations between anaesthetic inductions. Personal sampling was carried out from the anaesthetist's breathing zone and concentrations were also low (1.2 (0.8–2.1) for sevoflurane and 45.9 (10.1–261.6) for nitrous oxide. (*Br. J. Anaesth.* 1997; **79**: 342–345).

Key words
Anaethetics volatile, sevoflurane. Operating rooms, contamination.

Gaseous induction of anaesthesia is possible with sevoflurane in adults because of its low blood-gas solubility and non-irritant nature.[1] Several studies have demonstrated rapid induction of anaesthesia with high concentrations of the gas. Both tidal volume[2] and vital capacity[3] inductions have been tried successfully at high concentration with perhaps the latter technique being slightly faster and smoother. Gaseous induction with sevoflurane appears to be safe in patients for induction, but the effect on pollution levels in the anaesthetic room is not known.

This study was undertaken to determine pollution levels in the anaesthetic room concomitant with high concentration, triple vital capacity induction in adults using sevoflurane. An occupational exposure level of 20 ppm has been set by the manufacturers of sevoflurane. During three lists, nitrous oxide was monitored to assess the acceptability of using this agent in the fresh gas flow during induction.

Materials and methods

Environmental pollution was studied during eight consecutive orthopaedic lists where a relatively high turnover of patients was expected. Sevoflurane was monitored during five lists when there were 23 inductions, while nitrous oxide was monitored during three lists when there were 12 inductions. There were six personal samples obtained measuring sevoflurane concentrations and nine measuring nitrous oxide concentrations. Monitoring was performed in the anaesthetic room and all breathing systems were subject to active scavenging by a Venturi injector system operated by an 8 litre min^{-1} oxygen source on the anaesthetic machine. Consecutive gaseous inductions were performed with no i.v. inductions. Sevoflurane and nitrous oxide were used for maintenance of anaesthesia in theatre so that inadvertent spillage of anaesthetic gases could be monitored as this might affect background pollution levels.

Two methods of environmental monitoring were used, background sampling and personal sampling.

BACKGROUND ENVIRONMENTAL SAMPLING

Environmental pollution associated with the use of a Bain breathing system (co-axial Mapleson D) was examined. All inductions were performed in one of two anaesthetic rooms and air changes were measured formally in these rooms using sulphur hexafluoride and an infrared spectrometer. Twenty-five inductions were carried out in one anaesthetic room and 10 in the other.

Environmental monitoring of the anaesthetic gases was performed using a MIRAN 1B. This is a portable ambient air analyser which uses a single beam infrared spectrophotometer to measure background air pollution in working environments. Nitrous oxide was sampled at a wavelength of 4.68 μm and sevoflurane at 8.9 μm. The MIRAN was calibrated using the MIRAN closed-loop calibration

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J. E. HALL, MA, FRCA, T. A. OLDHAM, FRCA, S. PUGH, FRCA, M. HARMER, FRCA (Department of Anaesthetics and Intensive Care Medicine); K. A. HENDERSON, BSC (Health and Safety Department); University of Wales College of Medicine, Heath Park, Cardiff CF4 4XN. Accepted for publication: April 8, 1997.
Correspondence to J. E. H.

system before starting the study by introducing a known volume of anaesthetic agent into the MIRAN.

The MIRAN probe was positioned between 80 and 120 cm from the patient's head, behind and slightly to one side of the anaesthetist in an attempt to sample the highest concentrations of volatile agent. Monitoring was carried out for the whole theatre list to obtain a picture of the peaks and troughs throughout the day. Data were transferred onto a data logger and this information was then converted to graphical form.

The following gaseous induction techniques were used.

Sevoflurane monitoring

After preoxygenation, the patient was instructed to take a deep inspiration of 100% oxygen, and during the subsequent expiration, the inspired gas composition was changed to the induction mixture of 8% (dial) in oxygen. Induction then commenced with the patient taking three consecutive vital capacity breaths, the third breath being held for as long as possible. When patients were unable to hold this breath any longer, they were allowed to breathe normally. Patients were instructed in the induction technique before operation. Initially fresh gas flows of 9 litre min^{-1} were used, which were reduced to 6 litre min^{-1} after loss of consciousness. The high gas flow technique ensured a rapid increase in the inspired concentration of sevoflurane necessary for rapid induction. The time taken for the inspired concentration of sevoflurane to increase to greater than 7% was approximately 5–6 s. Inspired gas concentrations were measured using a Capnomac Ultima monitor (Datex, Helsinki, Finland) via a sampling cannula placed between the distal end of the breathing system and the face mask. Jaw relaxation was tested every 30 s after loss of consciousness and a laryngeal mask airway was inserted when this was achieved. During insertion of the laryngeal mask airway, the breathing system was placed on the pillow next to the patient's head with the fresh gas flow still running; 23 inductions were carried out using this technique.

Nitrous oxide monitoring

In inductions where nitrous oxide was monitored, the induction technique was as described above, except that the induction mixture, when commenced, was 8% sevoflurane carried in nitrous oxide and oxygen (ratio 2:1); 12 inductions were carried out using this technique.

Gaseous inductions were carried out by two of the authors (J. E. H. and S. P.). Both anaesthetists were familiar with the triple vital capacity breath induction technique.

PERSONAL SAMPLING

This was carried out using a 1-litre gas reservoir connected to a personal sampling pump. It was attached to the anaesthetist and sampled air directly from the breathing zone. Sampling was carried out over 1 h during which time one or two gaseous inductions were performed to give a single result. The gas sample was then analysed using the MIRAN 1B. Exposure of the anaesthetist during the hour of sampling was calculated taking into account the volume of the personal sampling system.

Results

Air changes in both anaesthetic rooms were within acceptable limits,[4] one room having 15 changes per hour (where 10 inductions were carried out) and the other 17 air changes per hour (where 25 inductions were carried out).

BACKGROUND EXPOSURE

Background exposures were low when assessed as time-weighted averages (TWA) (table 1). Conventionally it is usual to express TWA over an 8-h period but the operating lists were not so prolonged, and values were averaged over the period of each list. Peaks of both sevoflurane and nitrous oxide during induction of anaesthesia were followed rapidly by low background concentrations. All peaks for sevoflurane were less than 20 ppm and most were less than 10 ppm. Occasional higher results could be explained by an incident during anaesthesia (for example during induction with a sevoflurane peak of 17 ppm, the size 4 laryngeal mask airway was removed and replaced by a size 5 airway causing some extra pollution). There was more variability in the peak values for nitrous oxide, although TWA values were also below the occupational exposure standard (OES).

PERSONAL EXPOSURE

Personal sampling during induction and maintenance of anaesthesia revealed low exposure. One nitrous oxide personal sample appeared to be unusually high (261 ppm). This bag was removed at one point from the anaesthetist while still sampling and placed on the anaesthetic machine. It is possible that it came into contact with concentrated nitrous oxide during a circuit break at this time.

Table 1 Peak, personal reservoir sample and time weighted average gaseous concentrations (mean (range))

	Peak levels (ppm)	Time weighted average (ppm)	Personal reservoir sample concentration (ppm)
Sevoflurane	8.3	1.1	1.2
(5 lists, 23 inductions, 6 personal samples)	(4.1–17.0)	(0.6–1.7)	(0.8–2.1)
Nitrous oxide	172.4	17.3	45.9
(3 lists, 12 inductions, 9 personal samples)	(65–310)	(12–23)	(10.1–261.6)

Discussion

While there is at present no official OES for sevoflurane, it is a halogenated ether, similar to enflurane and isoflurane, both of which have an OES of 50 ppm.[5] Target compliance with this level is probably sensible. Abbott Laboratories, the manufacturers of sevoflurane, have suggested a limit of 20 ppm.[6] This was set to be 100 times lower than the level which would have any clinical effect (i.e. 2000 ppm). These two limits have been chosen arbitrarily, but the 20 ppm limit is conservative compared with levels for isoflurane and enflurane, although the OES for halothane is 10 ppm. With the 20 ppm limit in mind it seems that high concentration sevoflurane induction in adults complies with the environmental standard. Monitoring was also carried out during gaseous induction with sevoflurane carried in combined nitrous oxide and oxygen. The OES for nitrous oxide is 100 ppm, and the TWA complied with this

Using the personal sampling apparatus, samples were obtained directly from the breathing zone of the anaesthetist to provide a clearer picture of personal exposure. More marked increases in volatile concentration could have been expected, but this was not manifest and the anaesthetists received low exposures. There was one high result among the nitrous oxide samples which may have been caused by intraoperative breathing system disconnection.

The Mapleson A breathing system was used in an early gaseous induction study[7] and has been used subsequently[8] but it is probably not the best system for the vital capacity technique because of the need to prefill the breathing system. This necessitates changing from a separate preoxygenation system, probably causing environmental spillage. In addition, the technique is quite cumbersome, extra equipment is needed in theatre and the stopper on the system may dislodge causing further pollution. The use of high fresh gas flows with the Bain allows induction to be carried out with a single breathing system. The Bain can be used conveniently for gaseous induction without necessitating changing the system after preoxygenation. It was decided not to examine pollution associated with the circle system because this is used infrequently in the anaesthetic room in our own practice. Gaseous induction with a circle system would probably be economical to use and associated with low pollution, if anaesthesia was induced in theatre. The circle system has been used for halothane gaseous induction[9] and environmental monitoring would be of interest to hospitals using this breathing system for induction and in countries which do not use anaesthetic rooms.

The marked influence of individual anaesthetists on levels of environmental pollution has been demonstrated by Gray and Spence[10] who found that the anaesthetist's exposure varied by a factor of 17 on a day-to-day basis. The influence of different techniques cannot be underestimated and our highest sevoflurane peak was associated with change of a laryngeal mask airway. The anaesthetics in this study were conducted by two different anaesthetists who, although both familiar with the triple vital capacity gaseous induction technique, would inevitably use slightly different anaesthetic techniques. This variation aside, using the prescribed method, neither anaesthetist produced pollution of such levels that the OES values were contravened.

Anaesthetists are exposed constantly to low levels of volatile anaesthetic agents. Early epidemiological research which examined occupational health exposure was often poorly controlled. A large body of research has examined the biological effect of chronic exposure on animals. Work in rats has shown nitrous oxide to be associated with a lower implantation rate and a higher fetal death rate.[11] In addition, production of smaller rat litters and increased skeletal malformation have also been demonstrated.[12] Volatile agents have also been implicated in animal work with skeletal anomalies being demonstrated after 12-h exposure to 0.8% halothane in rats.[13] Extrapolation to humans is of course difficult, but by the late 1980s there was a sufficient body of evidence to negate the association between human developmental toxicity and nitrous oxide.[14] A 10-yr prospective study was undertaken by Spence,[15] the results of which have been partially reported to the Medical Research Council. Initial results would seem to suggest that anaesthesia is not associated with an occupational health risk.

The OES were set by the Health and Safety Executive to be well below the levels thought safe for animals. There may be little convincing evidence to show an association between low anaesthetic exposure and toxicity, but high levels do have an effect and it is sensible to maintain a low level of occupational exposure to any potentially toxic substance. The 1994 regulations of the control of substances hazardous to health and the occupational exposure standards for the four named anaesthetic agents have been enforced since January 1996 in an attempt to control the anaesthetist's working environment. It appears that gaseous induction with sevoflurane with or without nitrous oxide administered by the technique we have described complies with environmental standards and lack of compliance is not a bar to the potential of sevoflurane as a single agent anaesthetic.

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LABORATORY INVESTIGATIONS

Effect of haemoglobin concentration on brain oxygenation in focal stroke: a mathematical modelling study

F. DEXTER AND B. J. HINDMAN

Summary

Acute perioperative anaemia may affect neurological injury from permanent focal ischaemic insults. We modelled the opposing effects of haemodilution (increasing cerebral blood flow, decreasing arterial oxygen content) on oxygen availability and uptake in the ischaemic penumbra. First, we validated a mathematical model of regional cerebral oxygen uptake by using published arterial oxygen content and cerebral blood flow values from normal rabbits with progressive anaemia. Then we applied the model to the problem of interest (i.e. the ischaemic penumbra of a focal embolic stroke). We re-analysed published experimental data giving the cerebral blood flow response to anaemia in the ischaemic penumbra. Penumbral extraction reserves were nearly exhausted at a haemoglobin concentration of approximately 10 g 100 ml^{-1}. Oxygen uptake in the ischaemic penumbra decreased progressively when haemoglobin concentrations decreased to less than 10 g 100 ml^{-1}. We conclude that, given the available clinical and experimental literature, and until a suitable randomized clinical study has been performed, a haemoglobin concentration of 10 g 100 ml^{-1} is the rational transfusion "trigger" for the acutely anaemic stroke patient. (*Br. J. Anaesth.* 1997; **79**: 346–351).

Key words
Blood, haemoglobin. Brain, metabolism. Brain, blood flow. Brain, ischaemia. Blood, haemodilution. Complications, anaemia. Model, mathematical.

More than half a million adults undergo cardiac surgery in Europe and North America each year.[1] Modern cardiac surgery includes operative blood loss, deliberate haemodilution and the desire to limit homologous transfusion. Thus cardiac surgery patients often have haemoglobin concentrations of 7–9 g 100 ml^{-1} for several days after operation. Currently, 3–5% of cardiac surgery patients also sustain a perioperative cerebral infarction (stroke).[2 3] It is not known if the marked postoperative anaemia of cardiac surgery patients affects their neurological outcome. Laboratory[4–7] and clinical studies[8–11] have provided conflicting results. In some studies haemodilution improved neurological outcome[4 5 8 9]; by increasing cerebral blood flow (CBF), haemodilution may have improved oxygenation of marginally viable brain (the "ischaemic penumbra"). Other studies have found an adverse effect with haemodilution.[6 7 10 11] Under these circumstances, reduced arterial oxygen content may have more than offset increased CBF and resulted in a net reduction in oxygen delivery to the penumbra. In this study, we have modelled the opposing effects of haemodilution (increasing CBF, decreasing arterial oxygen content) on oxygen availability and uptake in the ischaemic penumbra.

Our goal in this study was to see if there was a haemoglobin concentration below which penumbral oxygenation would be impaired rather than improved. Until a suitable randomized clinical study has been performed, such a predicted haemoglobin concentration would be a rational "transfusion trigger" for the anaemic, normothermic stroke patient.

Materials and methods

We adapted our previously described mathematical model of cerebral oxygen transport.[12] We used this model to predict regional cerebral oxygenation in normal and penumbral brain as a function of arterial haemoglobin concentration. There are no human CBF data covering a wide range of haemoglobin concentrations in acute stroke. Thus we used CBF and cerebral metabolic rate for oxygen (CMR_{O_2}) data obtained from rabbits. CBF responses to haemodilution are known for this species, both in the presence[13] and absence[13 14] of acute cerebral infarction.

We assumed a constant blood and brain temperature of 37 °C. At 37 °C, the human oxyhaemoglobin dissociation curve is described by the following relationship[15]:

$$S_{O_2}=\{[23400\,(P_{O_2}^{3}+150\,P_{O_2})^{-1}]+1\}^{-1} \qquad (1)$$

where S_{O_2} (unitless) = fractional oxyhaemoglobin saturation and P_{O_2} (mm Hg) = oxygen partial pressure. Diffusion primarily limits oxygen transfer from

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FRANKLIN DEXTER, MD, PHD, BRADLEY J. HINDMAN, MD, Department of Anesthesia, University of Iowa, Iowa City, IA 52242, USA. Accepted for publication: March 26, 1997.
Correspondence to F. D.

haemoglobin to brain.[16] Hence we did not include chemical reaction kinetics in the model. The haemoglobin P_{50} of the rabbit (4.0 kPa) and Hill coefficient (2.8) are almost identical to those of humans (3.5 kPa and 2.9, respectively).[17 18] Therefore, human and rabbit oxyhaemoglobin saturation curves can be considered to be equivalent.

Net regional oxygen transport from blood to brain tissue (i.e regional brain oxygen uptake) is described using Fick's law of diffusion for a parallel plane layer geometrical configuration[19 20]:

$$\mathrm{rCMRO_2}= \left(\frac{11358}{27\times10^{-4}}\right)(2.9\times10^{-5}\times13\times(8.22\times10^{-4})\times Pec_{O_2}-Pin_{O_2} \qquad (2)$$

where $\mathrm{rCMR_{O_2}}$=regional $\mathrm{CMR_{O_2}}$ (ml O_2 100 g^{-1} min^{-1}), Pec_{O_2} (mm Hg)=regional end-capillary oxygen partial pressure and Pin_{O_2} (mm Hg)=regional interstitial oxygen partial pressure. The term 11 358 cm^2 100 g^{-1}=the sum of arteriole, capillary and venule surface areas available for oxygen exchange[21]; the term 27×10^{-4} cm=the sum of capillary and tissue thickness[20]; the term 2.9×10^{-5} ml O_2 ml^{-1} mm Hg^{-1}=oxygen solubility in brain at 37 °C[22]; the term 8.22×10^{-4} cm^2 min^{-1} specifies the net oxygen diffusion coefficient in blood and brain[23]; 13 (unitless) is a correction factor shown by Schacterle, Ribando and Adams to be necessary for Fick's law to attain the level of oxygen transport measured experimentally.[24] The correction is needed because oxygen diffuses intracellularly through areas of high solubility (i.e. lipid).[25] Thus this correction factor has been shown to come from the oxygen diffusion properties of lipids. As such, it is unlikely to be affected by changes in regional CBF, intracellular pH, etc, as may occur in the ischaemic penumbra. Also, the factor is unlikely to vary greatly among species.

$\mathrm{rCMR_{O_2}}$ can be determined by mass balance[19]:

$$\mathrm{rCMR_{O_2}}=\mathrm{rCBF}\ (1.34\ \mathrm{Hb}\ Sa_{O_2}+\alpha_{bl}\ Pa_{O_2}-1.34\ \mathrm{Hb}\ Sec_{O_2}-\alpha_{bl}\ Pec_{O_2}) \qquad (3)$$

where rCBF=regional CBF (ml $g^{-1}min^{-1}$), Hb=haemoglobin concentration (g 100 ml^{-1}); α_{bl}=oxygen solubility in blood (0.0029 ml O_2 100 ml^{-1} mm Hg^{-1}),[19] Sa_{O_2} (unitless)=arterial oxyhaemoglobin saturation, Pa_{O_2} (mm Hg)=arterial oxygen partial pressure and Sec_{O_2} (unitless)= cerebral end-capillary oxyhaemoglobin saturation. Our model is for cardiac surgery patients undergoing mechanical ventilation and therefore we used $Pa_{O_2}=100$ mm Hg and $Sa_{O_2}=1.0$ in all simulations.

Todd, Weeks and Warner recently reported that, in rats, brain haemoglobin concentration is less than systemic arterial haemoglobin concentration.[26] Other groups have not confirmed this finding.[27] Nevertheless, whole brain haemoglobin concentration can be less than systemic arterial and jugular haemoglobin concentrations, if erythrocytes travel through the capillary beds faster than plasma.[26] Thus the experimental findings of Todd, Weeks and Warner do not change the validity of mass balance for the amount of oxygen being delivered to and leaving the brain.[26] Equation (3) only uses haemoglobin concentration in this manner (i.e. to specify mass balance for oxygen for a region of brain).

Regional cerebral oxygen consumption varies with interstitial oxygen partial pressure[24 28]:

$$\mathrm{rCMRO_2}=\frac{3.5\times Pin_{O_2}}{Pin_{O_2}+2.0} \qquad (4)$$

Normal human $\mathrm{rCMR_{O_2}}$=3.5 ml O_2 100 g^{-1} min^{-1}.[29] The term 2.0 mm Hg specifies the interstitial oxygen partial pressure at which $\mathrm{rCMR_{O_2}}$ is 50% of normal.[29] Thus, as interstitial oxygen partial pressure increases, $\mathrm{rCMR_{O_2}}$ asymptotically approaches a maximal (normal) value. Back, Kohno and Hossmann found that brain interstitial oxygen partial pressures were 28 mm Hg in normothermic rats.[30] Substituting this value into equation (4) gives a $\mathrm{rCMR_{O_2}}$ value of 93% of normal. We consider 93% to be a value clinically indistinguishable from normal. Conveniently, 3.5 ml O_2 100 g^{-1} min^{-1} is not only a normal $\mathrm{rCMR_{O_2}}$ value for awake humans, but also in anaesthetized rabbits.[31] This equivalence allows the use of rCBF and $\mathrm{rCMR_{O_2}}$ data from anaesthetized rabbits with acute embolic stroke to estimate the effect of anaemia on the human ischaemic penumbra.

We first tested the validity of the model; to do this we checked that the model predicted the effect of haemodilution on cerebral oxygenation ($\mathrm{CMR_{O_2}}$, oxygen extraction) in normal brain. We used data from Todd and colleagues.[14] They decreased the haemoglobin concentration of anaesthetized rabbits from 13 to 4.5 g 100 ml^{-1} and measured changes in CBF, oxygen extraction and $\mathrm{CMR_{O_2}}$. We inserted their values for mean haemoglobin concentration, arterial oxygen contents and CBF into our model. Algebraic equations (1)–(4) were numerically solved simultaneously.[32] Solutions for $\mathrm{CMR_{O_2}}$ were constrained to be less than or equal to the maximal (normal) $\mathrm{CMR_{O_2}}$.[32] Iterations were continued until $\mathrm{CMR_{O_2}}$ was calculated to within 0.01%. We compared predicted $\mathrm{CMR_{O_2}}$ and oxygen extraction ratios with those measured by Todd and colleagues.[14]

Next we modelled the effect of anaemia on penumbral oxygenation; to do this we used the CBF data of Korosue and Heros.[13] They measured rCBF in the ischaemic penumbra of rabbits after embolic stroke and acute isovolaemic haemodilution, and simultaneously measured rCBF in the non-embolized contralateral hemisphere:

$$\mathrm{rCBF}=\begin{cases}0.384\ (-7\ 4\ (1.34\ \mathrm{Hb}\ Sa_{O_2}+\alpha_{bl}Pa_{O_2})+212.7), & \text{normal brain} \\ 0.201\ (-3.0\ (1.34\ \mathrm{Hb}\ Sa_{O_2}+\alpha_{bl}Pa_{O_2})+150.4), & \text{ischaemic penumbra}\end{cases} \qquad (5)$$

As before, algebraic equations (1)–(4) were solved simultaneously to determine $\mathrm{rCMR_{O_2}}$ and oxygen extraction as a function of haemoglobin concentration.

Results

We first used data from Todd and colleagues[14] to test the model. Table 1 gives measured and

Table 1 Comparison of model predictions with data from Todd and colleagues.[14] Model parameters are the mean experimental values which were substituted into the mathematical model. The maximum normal cerebral metabolic rate for oxygen ($CMRo_2$) was set equal to the maximum observed mean $CMRo_2$ (4.0 ml O_2 100 g^{-1} min^{-1}), rather than 3.5 ml O_2 100 g^{-1} min^{-1}, as used in equation (4). Measured oxygen extraction ratio and $CMRo_2$ are reported as mean (SD) (n=6). CBF=Cerebral blood flow

Model parameters			Measured		Predicted	
Haemoglobin concn (g 100 ml^{-1})	Arterial oxygen content (ml O_2 100 ml^{-1})	CBF (ml 100 g^{-1} min^{-1})	Oxygen extraction ratio (%)	CMR_{O_2} (ml O_2 100 g^{-1} min^{-1})	Oxygen extraction ratio (%)	CMR_{O_2} (ml O_2 100 g^{-1} min^{-1})
13	18	44	43 (11)	3.3 (0.9)	47	3.7
10	14	49	50 (11)	3.4 (1.1)	55	3.7
6.6	9.4	60	67 (4)	3.8 (0.4)	65	3.6
4.5	6.6	81	68 (5)	3.6 (0.4)	67	3.6

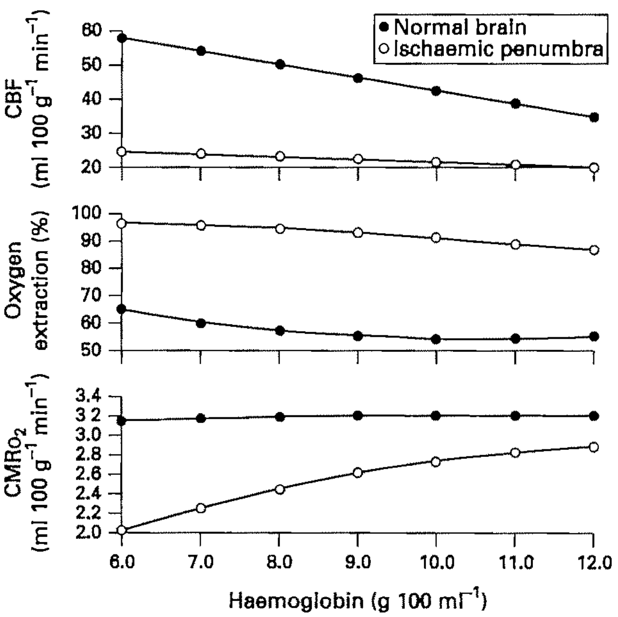

Figure 1 Dependence of oxygen extraction and cerebral metabolic rate ($CMRo_2$) on cerebral blood flow (CBF) and haemoglobin concentration. The mathematical model predicts regional oxygen extraction and cerebral metabolic rate for oxygen (CMR_{O_2}) given regional CBF and haemoglobin concentration. Experimental data[13] give regional CBF as a function of haemoglobin concentration, in normal brain and in the ischaemic penumbra of a middle cerebral artery infarction (top). CBF and haemoglobin concentration are then used as inputs in the mathematical model to predict regional oxygen extraction (middle) and regional CMR_{O_2} (bottom).

predicted values of CMR_{O_2} and oxygen extraction during acute isovolaemic haemodilution in rabbits. Our model predictions were well within the error of their measurements. Hence, our model accurately predicted brain oxygen extraction and the resulting CMR_{O_2} in the presence of acute isovolaemic haemodilution. These data also show that, in normal brain, the increase in CBF with haemodilution does not fully compensate for decreased arterial oxygen content. Thus to maintain normal CMR_{O_2}, the brain increases oxygen extraction. The increase in extraction is sufficient to preserve CMR_{O_2}, even in the presence of very severe anaemia (haemoglobin concentration as low as 4 g100 ml^{-1}).

Having validated our model, we next applied it to the problem of interest. In figure 1 (top), we show measured[13] rCBF as a function of arterial haemoglobin concentration. Haemodilution increased CBF in both normal brain and ischaemic penumbra. However, the magnitude of the increase was much less in the ischaemic penumbra than that in normal brain (fig. 1, top). In the non-ischaemic brain, reduction in haemoglobin concentration from 12 to 6 g100 ml^{-1} caused a 65% increase in CBF (or 23 ml 100 g^{-1} min^{-1}). However, in the ischaemic penumbra, the same reduction in haemoglobin concentration caused CBF to increase by only 24% or 5 ml 100 g^{-1} min^{-1}.

The measured CBF *vs* haemoglobin relationships from figure 1 were used as inputs in our mathematical model. Regional brain oxygen uptake (i.e. CMR_{O_2}) was predicted from the haemoglobin concentration (fig. 1). The model predicted that, at a haemoglobin concentration of 12 g 100 ml^{-1}, $rCMR_{O_2}$ in the ischaemic penumbra is only slightly (10%) less than that in normal tissue (2.9 *vs* 3.2 ml 100 g^{-1} min^{-1}) (fig. 1, bottom), because of greater oxygen extraction (fig. 1, middle). This model prediction is consistent with experimental studies of regional oxygen metabolism in focal cerebral ischaemia. Acutely, penumbral CMR_{O_2} has been found to be only 7–20% less than that of non-ischaemic brain.[33–35]

For the non-ischaemic brain, the model predicted that increases in CBF from anaemia do not fully compensate for decrease in arterial oxygen content. A moderate increase in oxygen extraction is needed to maintain normal brain oxygen uptake (fig. 1, middle). However, with this increase, normal brain maintains oxygen uptake, even with marked anaemia. As stated before, this model prediction is consistent with the study of Todd and colleagues[14] of isovolaemic anaemia in rabbits (table 1).

In contrast, the model predicted that, in the ischaemic penumbra, increased CBF (fig. 1, top) and oxygen extraction (fig. 1, middle) are *not* sufficient (fig. 1, bottom) to compensate for decreases in arterial oxygen content. Oxygen uptake ($rCMR_{O_2}$) in the ischaemic penumbra decreased progressively with greater anaemia. For example, at a haemoglobin concentration of 6 g 100 ml^{-1}, predicted oxygen uptake in the ischaemic penumbra was 36% less than that in non-ischaemic brain. Our model predicted that anaemia of less than 10 g 100 ml^{-1} decreased oxygen availability to penumbral tissue.

Discussion

PREVIOUS CLINICAL AND LABORATORY STUDIES

Cardiac surgery patients sustain perioperative cerebral infarction at a rate exceeding 3%.[23] They are also routinely haemodiluted to haemoglobin concentrations of 7–9 g 100 ml^{-1}. It is not clear if, after operation, red blood cell transfusion may improve neurological outcome. There is evidence to suggest that it may. Neuropsychological impairment 9 days after cardiac surgery is associated with haemoglobin concentrations of less than 10 g 100 ml^{-1} in the first 12 h after surgery.[36] Also, acute neurological and neuropsychological outcome is significantly worse in cardiac surgery patients with the greatest perioperative reductions in haemoglobin concentration.[37] Lee and colleagues used a middle cerebral artery occlusion model in dogs.[7] They found that infarction volumes were less in animals with a haemoglobin concentration of 10 g 100 ml^{-1} than in those with a concentration of 8 g 100 ml^{-1}. Similarly, we recently used an embolic stroke model in rabbits.[6] Animals allocated randomly to a haemoglobin concentration of 6 g 100 ml^{-1} had larger infarction volumes than those allocated to a haemoglobin concentration of 11 g 100 ml^{-1}. Collectively, these studies suggest that acute anaemia can exert a detrimental effect on neurological outcome, especially when postoperative haemoglobin concentrations are less than 10 g 100 ml^{-1}. Our model predictions strongly support this suggestion.

PENUMBRAL OXYGEN UPTAKE

Our model predicted that at haemoglobin concentrations of 10–12 g 100 ml^{-1}, increased CBF and oxygen extraction were sufficient to permit penumbral oxygen uptake to remain nearly normal. As stated previously, this result is consistent with the experimental literature. However, the model predicted that there is an abrupt decrease in penumbral oxygen uptake when haemoglobin concentrations decrease to less than 10 g 100 ml^{-1}. This is because, in the ischaemic penumbra, increases in CBF and oxygen extraction are insufficient to compensate for decreases in arterial oxygen content when haemoglobin concentrations are less than 10 g 100 ml^{-1}. Penumbral oxygen extraction reserves are nearly exhausted even after only moderate anaemia (haemoglobin concentration of 12 g 100 ml^{-1}). Progressively greater degrees of anaemia limit oxygen uptake in the ischaemic tissue.

Optimal management of patients with acute perioperative stroke should include efforts to support penumbral oxygenation. Penumbral tissue sustains a series of membrane depolarizations in the hours after onset of focal ischaemia.[30 38–41] These depolarizations, lasting 5–10 min,[30] do not change penumbral CBF, but appear to transiently increase cerebral metabolism. The increase in cerebral metabolism is probably a result of the increased ion pump activity needed to re-establish transmembrane ionic homeostasis.[40 42] Therefore, ischaemic membrane depolarizations increase penumbral energy requirements, exacerbating the mismatch between metabolic demand and substrate supply.[30] This mismatch may explain why the number and duration of depolarizations correlate(s) with final infarction volume.[38 39 41] Haemoglobin concentrations less than 10 g 100 ml^{-1} progressively limit oxygen availability to the penumbra. Thus marked anaemia seems likely to slow restoration of ionic homeostasis. Doing so may promote a more rapid deterioration of the penumbra. Rapid deterioration of the penumbra converts what was potentially salvageable tissue into infarct.[41]

ROLE OF MATHEMATICAL MODELLING

Factors other than haemoglobin concentration have important effects on neurological outcome, such as the timing of therapy, species studied, vascular territories involved and arterial pressure. These factors, almost certainly, are responsible for some of the discrepancies between previous studies.[4–11] The regional CBF data of Korosue and Heros[13] were obtained at normal arterial pressures and temperatures. Thus our model predictions apply to the condition of normotension and normothermia. On the other hand, the mechanism of CBF response to haemodilution (e.g. viscosity *vs* metabolism) is of no importance to our model predictions. CBF is an independent variable in the mathematical model (eqn (5)). The magnitude of the CBF response to haemodilution is important and may depend on both the viscosity characteristics of the haemodilutant and arterial oxygen content.[43] Korosue and Heros used plasma to haemodilute their rabbits,[13] while Todd and colleagues used hetastarch.[14] Our results apply to acute haemodilution with similar substances. Haemodilution with cross-linked haemoglobin would, for example, be expected to give results different from those predicted by our model.[43]

The multiple factors that can influence neurological outcome demonstrate the advantage of using mathematical modelling. We focused only on haemoglobin concentration (fig. 1). The mathematical model used in this study was intentionally simplistic with respect to the process of oxygen diffusion from blood to brain. Decisions to apply existing models to this study were based on four limitations. First, terms must have been measured under the conditions of focal embolic stroke. The only values that have been measured reliably are regional CBF (i.e. Korosue and Heros' rabbit data[13]). Additional dependent variables, such as intracapillary red blood cell spacing and spatial heterogeneity of red blood cell flow, are not available. Additional experimental data are not likely to be forthcoming soon. Tissue P_{O_2} electrodes could be placed into the ischaemic penumbra. However, as equation (4) shows, tissue P_{O_2} and regional CMR_{O_2} are not equivalent. The model makes predictions for the effect of haemodilution on regional CMR_{O_2}, not tissue P_{O_2}. Furthermore, to identify the ischaemic penumbra, simultaneous regional CBF measurements would be needed. The only technique that can accomplish both of these requirements is positron emission tomographic scanning. Second, CBF data were available only for gross regions of the brain,[13] not at the microcirculatory level. Thus a model based on space-averaged oxygen tensions was necessary. Third, we used CBF and CMR_{O_2} data obtained from rabbits. Korosue and Heros[13] also studied rabbits. Rabbits and humans share many key physiological characteristics (cerebrovascular anatomy, arterial pressure, haemoglobin concentration, CBF, CMR$_{O_2}$, haemoglobin P$_{50}$ and co-operativity). Hence, conclusions regarding cerebrovascular physiology derived from rabbit data are likely to be applicable to humans. Fourth, not all of the biophysical variables we needed were available for rabbits or humans. Biophysical transport variables from species other than rabbits would not be expected to differ significantly. Therefore, we doubt that this limitation had much effect on the simulation results, at least qualitatively. Additional model complexity would not have compensated for this latter weakness. Thus increased model complexity would not have substantively increased model accuracy. However, despite our model's limitations, *it successfully predicted* the data of Todd and colleagues[14] (table 1). The basic processes of regional brain oxygen uptake alone can *accurately predict* the effect of anaemia on oxygen extraction. We used the mathematical model to make clinically significant predictions only *after we had verified* the validity of the model.

CLINICAL SIGNIFICANCE

An American Society of Anesthesiologist's task force recently published practice guidelines for blood component therapy.[44] The task force concluded that red blood cell transfusion is rarely indicated when the haemoglobin concentration exceeds 10 g 100 ml^{-1} but is almost always appropriate when it is less than 6 g 100 ml^{-1}. In addition, the task force concluded that "the determination of whether intermediate haemoglobin concentrations (6–10 g 100 ml^{-1}) justify or require red blood cell transfusion should be based on the patient's risk for complications of inadequate oxygenation." Our results showed that, in the presence of an acute focal stroke, penumbral oxygenation is likely to be inadequate at haemoglobin concentrations less than 10 g 100 ml^{-1}. Our model predictions do not stand in isolation; they are consistent with other clinical[36 37] and laboratory[6 7] studies. All of these studies suggest that haemoglobin concentrations less than 10 g 100 ml^{-1} worsen neurological outcome after embolic stroke. We conclude that, given the available clinical and experimental literature, and until a suitable randomized clinical study has been performed, a haemoglobin concentration of 10 g 100 ml^{-1} is the rational transfusion "trigger" for the acutely anaemic stroke patient.

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Actions of tramadol, its enantiomers and principal metabolite, O-desmethyltramadol, on serotonin (5-HT) efflux and uptake in the rat dorsal raphe nucleus

T. A. BAMIGBADE, C. DAVIDSON, R. M. LANGFORD AND J. A. STAMFORD

Summary

Tramadol is an atypical centrally acting analgesic agent with relatively weak opioid receptor affinity in comparison with its antinociceptive efficacy. Evidence suggests that block of monoamine uptake may contribute to its analgesic actions. Therefore, we have examined the actions of (±)-tramadol, (+)-tramadol, (−)-tramadol and O-desmethyltramadol (M1 metabolite) on electrically evoked 5-HT efflux and uptake in the dorsal raphe nucleus (DRN) brain slice, measured by fast cyclic voltammetry. Racemic tramadol and its (+)-enantiomer (both 5 μmol litre^{-1}) significantly blocked DRN 5-HT uptake (both $P<0.05$) and increased stimulated 5-HT efflux ($P<0.01$ (±)-tramadol; $P<0.05$ (+)-tramadol). The (−)-enantiomer and metabolite, O-desmethyltramadol, were inactive at the concentration tested (5 μmol litre^{-1}). For both (±)-tramadol and the (+)-enantiomer, the action on 5-HT efflux preceded an effect on 5-HT uptake, suggesting that uptake block was not the cause of the increased 5-HT efflux and that tramadol might therefore have a direct 5-HT releasing action. This activity, at clinically relevant concentrations, may help to explain the antinociceptive efficacy of tramadol despite weak μ opioid receptor affinity and adds to evidence that tramadol exerts actions on central monoaminergic systems that may contribute to its analgesic effect. (*Br. J. Anaesth.* 1997; **79**: 352–356).

Key words
Analgesics opioid, tramadol. Serotonin (5-hydroxytryptamine). Model, rat. Measurement techniques, voltammetry.

Tramadol is a centrally acting analgesic agent, effective in the treatment of moderate to moderately severe pain with a relatively low addiction potential.[1] A striking feature of the pharmacology of tramadol is its relatively weak opioid receptor affinity in comparison with its antinociceptive efficacy, indicative of the involvement of other mechanisms. Interestingly, its antinociceptive action in some animal models is only partially antagonized by naloxone,[2] strongly suggesting a non-opioid component to its analgesic potency. Furthermore, tramadol has an active metabolite, O-desmethyltramadol.[3]

Analgesia can be achieved both centrally and peripherally by interference with a variety of neurotransmitter systems. In particular, the control of pain is subject to descending modulation by brainstem cell groups such as the locus coeruleus/subcoeruleus and raphe complex.[4] These nuclei contain mainly noradrenaline and serotonin (5-HT), respectively.

Drugs that block noradrenaline uptake (such as desipramine) or that stimulate α_2 adrenoceptors (e.g. clonidine) are useful adjuncts to standard analgesic therapy in intractable pain and are also analgesic in their own right. Tramadol has been shown to block noradrenaline uptake in cortical synaptosomes and brain slices[5] thereby increasing noradrenaline efflux.[6] This and the fact that α_2 adrenoceptor blockade reduces its analgesic efficacy[7 8] indicates that enhancement of noradrenaline function contributes significantly to its analgesic profile.

The involvement of 5-HT in the descending control of pain is also widely recognized[4] and tramadol has been shown to enhance basal efflux of [^{3}H]-5-HT in frontocortical synaptosomes.[9] Tramadol also blocks 5-HT uptake[10] and it is thus possible that the effects of tramadol on cortical 5-HT efflux are mediated via uptake blockade. However, the synaptosome is such a highly reduced system, devoid of the transmitter interactions found *in vivo,* that it is not easy to draw conclusions on the relationship between 5-HT efflux and uptake inhibition.

Therefore, we chose to examine the actions of tramadol on 5-HT efflux and uptake in the dorsal raphe nucleus (DRN) brain slice, for four reasons. First, the dorsal raphe is part of the brainstem raphe complex and has been shown to have a role in the descending control of pain.[11] Second, the brain slice retains much of the local synaptic integrity and interactions of the whole animal while being easier to manipulate. Third, drug concentrations may be controlled precisely *in vitro,* thus allowing the elimination of pharmacokinetic considerations that

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TIMOTHY A. BAMIGBADE, RICHARD M. LANGFORD, Department of Anaesthesia, St Bartholomew's Hospital, West Smithfield, London EC1A 7BE COLIN DAVIDSON, JONATHAN A. STAMFORD, Anaesthetics Unit (Neurotransmission Laboratory), Royal London Hospital, Whitechapel, London E1 1BB, UK. Accepted for publication: April 2, 1997.

Correspondence to J. A. S.

might confound data interpretation. Finally, the consequences of metabolism to active (or inactive) metabolites in the whole animal are excluded; this is particularly pertinent for tramadol.

Materials and methods

Fast cyclic voltammetry (FCV) at carbon fibre microelectrodes was used to determine the effects of tramadol, its enantiomers and principal metabolite on electrically stimulated 5-HT efflux and uptake in rat DRN brain slices. No Home Office-regulated procedures on live animals were performed.

PREPARATION OF SLICES OF THE RAT DORSAL RAPHE NUCLEUS

Male Wistar rats (150±25 g) were stunned and killed by rapid cervical dislocation. No prior anaesthesia was administered. The brain was excised rapidly and irrigated with ice-cold (−1 to +1 °C) artificial cerebrospinal fluid (aCSF). A Campden 752M vibratome was used to prepare 350-μm thick brainstem slices (+1.0 to +1.3 mm *vs* the interaural line[12]) containing the DRN (seen as a dove-shaped translucent area, ventral to the cerebral aqueduct). The brain slice was secured in a 1-ml volume superfusion-type brain slice tissue bath[13] by a nylon mesh drawn over a stainless steel grid. The internal temperature of the chamber was maintained at 32 °C and the slice was superfused with oxygenated (95% oxygen–5% carbon dioxide) aCSF at 1 ml min^{-1} throughout the experiment. Artificial CSF consisted of NaCl 124 mmol litre^{-1}, $NaHCO_3$ 25 mmol litre^{-1}, (+)-glucose 11 mmol litre^{-1}, KCl 2 mmol litre^{-1}, $CaCl_2$ 2 mmol litre^{-1}, $MgSO_4$ 2 mmol litre^{-1} and KH_2PO_4 1.25 mmol litre^{-1}.

MEASUREMENT OF 5-HT EFFLUX AND REUPTAKE BY FAST CYCLIC VOLTAMMETRY

A glass-coated carbon fibre (8 μm in diameter, 50 μm in length) recording electrode[14] was inserted 80 μm below the surface of the slice, approximately 200 μm from a bipolar tungsten stimulating electrode (A-M Systems, Seattle, USA). Figure 1A shows the basic set-up. The auxiliary (a 0.5-mm diameter stainless steel wire) and reference (Ag/AgCl cylinder) electrodes were positioned at a convenient location in the chamber.

Quantitative real time efflux of 5-HT was measured using FCV, as previously described.[15] An input voltage (1.5 cycles of a triangular waveform, −1.0 to +1.4 V *vs* Ag/AgCl, scan rate of 480 V s^{-1}) was applied to the potentiostat (Millar Voltammetric Analyser, PD Systems, West Molesey, UK) every 500 ms. The working electrode was disconnected between scans. The current output of the carbon fibre microelectrode was displayed on a digital storage oscilloscope (Nicolet 310DD). Background (charging) current signals before a stimulation were saved and subtracted from those obtained after a stimulus. Subtraction of one current signal from the other yielded the current caused by 5-HT oxidation and its subsequent reduction. A sample and hold circuit monitored the current at the oxidation potential for 5-HT (+570 mV *vs* Ag/AgCl). Its output was displayed on a chart recorder and stored on a microcomputer using CED (Cambridge Electronic Design) "Chart" software.

ELECTRICAL STIMULATION OF 5-HT RELEASE

All electrical stimulations were generated with standard Neurolog modules and applied to the stimulating electrode via an NL 800 constant current isolator. The slice was allowed to equilibrate in the chamber for at least 1 h before stimulation was conducted. 5-HT efflux was evoked by trains consisting of 20 pulses (0.1 ms duration, 10 mA constant current at 100 Hz) applied every 10 min.

On each stimulation, two variables were recorded: 5-HT efflux and uptake (see fig. 1B). 5-HT efflux was taken as the peak extracellular 5-HT concentration attained after stimulation. On cessation of stimulation, 5-HT was removed from the extracellular space by uptake. The "half-time" ($T_{1/2}$) of 5-HT uptake (the time taken for the extracellular 5-HT concentration to decrease to half of the peak concentration attained) was used as an (reciprocal) estimate of the rate of 5-HT uptake.

EXPERIMENTAL PROCEDURE

After three stable consecutive 5-HT efflux events were obtained (a control period of 30 min), the agent to be studied (at a concentration of 5 μmol litre^{-1}) was added to the superfusate for 2 h. Five treatment groups were compared: (±)-tramadol, (+)-tramadol, (−)-tramadol, O-desmethyltramadol (M1 metabolite) and control. Controls received aCSF. Group sizes were: (±)-tramadol (n=5 slices), (+)-tramadol (n=6), (−)-tramadol (n=6), O-desmethyltramadol (n=7) and control (n=5).

DRUGS

(±)-Tramadol, (+)-tramadol, (−)-tramadol and O-desmethyltramadol were gifts from Grünenthal GmbH (Germany). Stock solutions of each drug were prepared in distilled water. Subsequent dilutions were made in aCSF.

STATISTICAL ANALYSIS

All drug effects on 5-HT efflux and reuptake were plotted against time. The area under the curve was calculated for each individual experiment and means (SEM) were determined for each series of experiments. The data for (±)-tramadol, (+)-tramadol, (−)-tramadol and O-desmethyltramadol were tested for statistical significance compared with the control group using one-way analysis of variance (ANOVA) with *post hoc* application of Dunnett's test.

Results

Electrical stimulation (20 pulses, 0.1 ms, 100 Hz) in the DRN evoked efflux of 5-HT that was detected at

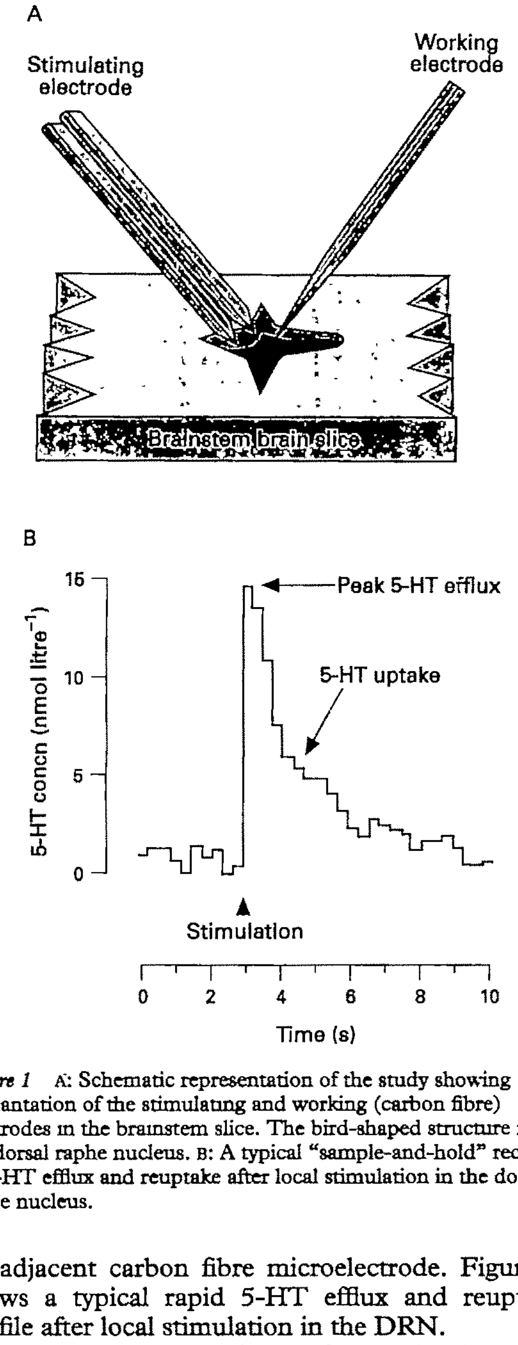

Figure 1 A: Schematic representation of the study showing implantation of the stimulating and working (carbon fibre) electrodes in the brainstem slice. The bird-shaped structure is the dorsal raphe nucleus. B: A typical "sample-and-hold" record of 5-HT efflux and reuptake after local stimulation in the dorsal raphe nucleus.

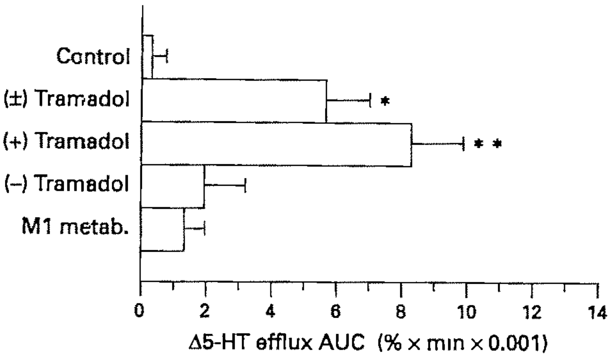

Figure 2 Effects of tramadol, its enantiomers and metabolite on stimulated 5-HT efflux in the rat dorsal raphe nucleus slice. Data are expressed as changes in the area under the 5-HT efflux *vs* time curve, relative to the pre-drug period. All values are mean (SEM) (n=5–7). $^{*}P<0.05$, $^{**}P<0.01$ *vs* control (Dunnett's test).

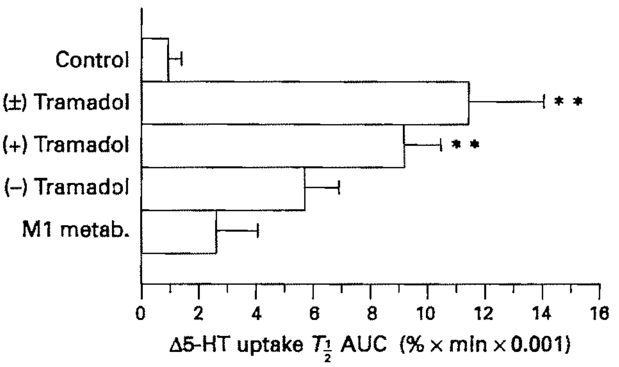

Figure 3 Effects of tramadol, its enantiomers and metabolite on 5-HT uptake half-time ($T_{1/2}$) in the rat dorsal raphe nucleus slice. Data are expressed as changes in the area under the 5-HT uptake $T_{1/2}$ *vs* time curve, relative to the pre-drug period. All values are mean (SEM) (n=5–7). $^{**}P<0.01$ *vs* control (Dunnett's test).

an adjacent carbon fibre microelectrode. Figure 1 shows a typical rapid 5-HT efflux and reuptake profile after local stimulation in the DRN.

Figure 2 shows the effects of tramadol, its enantiomers and main metabolite on stimulated 5-HT efflux. Data are expressed as mean (SEM) post-drug incremental area under the curve. (±)-Tramadol and its (+)-enantiomer significantly increased 5-HT efflux relative to aCSF controls ($P<0.05$ and $P<0.01$, respectively; Dunnett's test). The (−)-enantiomer and O-desmethyltramadol had no significant effect compared with control.

Figure 3 shows the effects of tramadol, its enantiomers and metabolite on 5-HT uptake $T_{1/2}$. As before, data are expressed as mean (SEM) post-drug incremental area under the curve. Similarly, the racemic mixture and (+)-enantiomer significantly slowed 5-HT reuptake (both $P<0.01$ *vs* control; Dunnett's test). O-desmethyltramadol and the (−)-enantiomer were inactive.

Figure 4 shows the time course of the effects of the active drugs, (±)-tramadol and (+)-tramadol, on stimulated 5-HT efflux and uptake $T_{1/2}$. For both (±)-tramadol and (+)-tramadol, there was a temporal dissociation between their effects on 5-HT efflux and uptake. In both cases, the drug effects on 5-HT efflux occurred before changes in 5-HT reuptake $T_{1/2}$.

Discussion

Release of neurotransmitter from isolated tissues maintained *in vitro* has long been a popular means of evaluating monoaminergic uptake mechanisms.[16] However, problems with this technique have been highlighted regarding its applicability to neurotransmitter release within small anatomical regions in the brain. Furthermore, the neurotransmitter pool is frequently labelled with tritium which assumes, probably incorrectly, that release of the radiolabel accurately reflects true neurotransmitter release.[17] We have therefore used FCV at carbon fibre microelectrodes to study the effects of racemic tramadol, its enantiomers and the major human metabolite, O-desmethyltramadol, on *endogenous* 5-HT neurotransmission in the DRN, a key nucleus in the regulation of afferent nociceptive transmission. An FCV scan takes only milliseconds and can be repeated many times per second, thus giving real time detection of neurotransmitter. This high

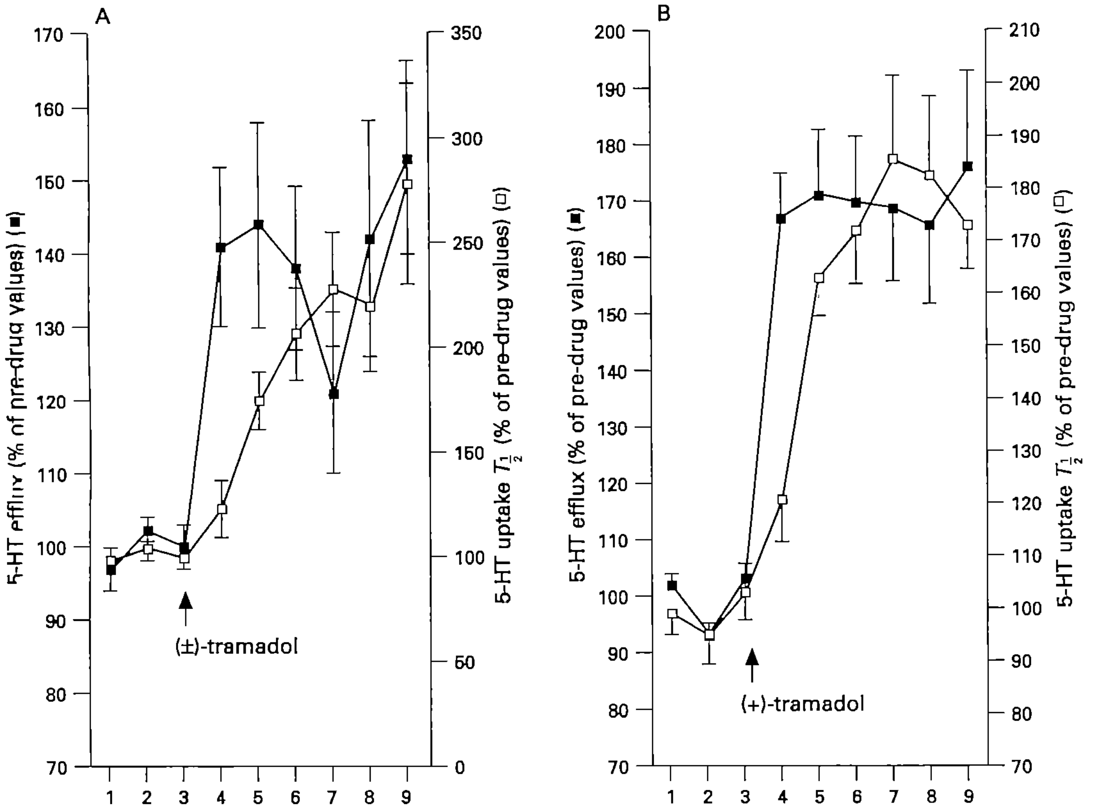

Figure 4 A: Time course of effects of (±)-tramadol 5 μmol litre on stimulated 5-HT efflux and 5-HT uptake half-time ($T_{1/2}$) in the rat dorsal raphe nucleus slice. B: Time course of effects of (+)-tramadol 5 μmol litre on stimulated 5-HT efflux and 5-HT uptake half-time ($T_{1/2}$) in the rat dorsal raphe nucleus slice. All data are mean (SEM) (n=6).

temporal resolution allows the relationship between 5-HT efflux and uptake to be determined precisely (see fig. 1).

In each case the drugs were applied at a concentration of 5 μmol litre^{-1}. This approximates to the plasma concentration of tramadol after a therapeutically effective dose.[18] Both (±)-tramadol and the (+)-enantiomer significantly enhanced stimulated 5-HT efflux in the DRN at this concentration. Neither (−)-tramadol nor the M1 metabolite, O-desmethyltramadol, had any effect (fig. 2). A qualitatively similar picture was obtained for the effects on 5-HT uptake (fig. 3). Again, both the (+)-enantiomer and the racemate were effective while the metabolite was devoid of action. Of interest, (−)-tramadol delayed 5-HT uptake in some slices although the group data were not statistically significant.

These findings are broadly consistent with the literature. Tramadol inhibited 5-HT reuptake, the (+)-enantiomer being the active form.[9] The hint of an effect on uptake with (−)-tramadol also supports the findings of other studies, using synaptosomes and radiolabelled neurotransmitter, indicating that it has approximately 25% of the activity of the (+)-enantiomer on the serotoninergic system.[9]

De-methylation of tramadol resulted in a marked reduction of activity on 5-HT reuptake inhibition. This is interesting for two reasons. First, the M1 metabolite is an effective analgesic and probably contributes significantly to the clinical profile of tramadol[1], presumably via μ opioid receptors.[3] Second, it is clear that the O-methyl function of the parent drug is therefore a structural determinant of 5-HT uptake block by tramadol.

As only those drugs that blocked 5-HT uptake —the (+)-enantiomer and the racemate—also increased 5-HT efflux, there is a prima facie case that uptake block is the *cause* of increased 5-HT efflux. However, such a conclusion is erroneous as the increase in 5-HT efflux after tramadol *preceded* reduced uptake (fig. 4). For both (±)-tramadol and its (+)-enantiomer, the effects on 5-HT efflux were essentially maximal on the first post-drug stimulation. Effects on 5-HT uptake $T_{1/2}$ did not reach maximum until considerably later.

Furthermore, with paroxetine, the effect on 5-HT reuptake is much greater than that on 5-HT efflux because of activation of negative feedback mechanisms reducing efflux.[15] Conversely, the effects of (+)-tramadol on 5-HT efflux and reuptake were of a similar magnitude.

The rapid effect of racemic tramadol and its (+)-enantiomer on 5-HT efflux cannot be caused by 5-HT$_1$ autoreceptor block as the choice of short-duration stimulation variables precludes activation of the autoreceptor during the stimulation train.[19] Furthermore, we have shown previously that the potent 5-HT$_{1A}$ antagonist WAY 100135 did not increase 5-HT efflux in this experimental procedure.[15]

Hence it appears that tramadol may have a direct releasing action. Other studies have shown that the tramadol-induced increase in 5-HT efflux does not occur if 5-HT reuptake sites are blocked by 6-nitroquipazine, before tramadol administration.[9]

This suggests that tramadol can compete with 5-HT for the uptake mechanism and, when inside the presynaptic terminal, increase stimulation-evoked 5-HT release. A direct effect on 5-HT release, dissociated from reuptake inhibition, may be important to the multimodal analgesic actions of tramadol. It is unlikely that opioid receptor activation is responsible for the 5-HT releasing action observed with (+)-tramadol and the racemate as the M1 metabolite had no 5-HT releasing action despite being a more potent opioid than the parent drug.[3]

In conclusion, both racemic tramadol and its (+)-enantiomer blocked DRN 5-HT uptake and increased stimulated 5-HT efflux. The temporal dissociation between these actions suggests that uptake blockade was not the cause of the increased 5-HT efflux and that tramadol might therefore have a direct 5-HT releasing action. It should nevertheless be remembered that we have only examined a single, albeit clinically relevant, concentration of tramadol and it would be interesting to examine such actions over an extended concentration range. Nevertheless, the activity of such mechanisms at clinically pertinent concentrations may help explain the antinociceptive efficacy of tramadol despite weak μ opioid receptor affinity. This study adds to evidence that tramadol exerts actions on central monoaminergic systems and that this mechanism may contribute to its analgesic effect.

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Dopamine and intestinal mucosal tissue oxygenation in a porcine model of haemorrhage

R. GERMANN, M. HAISJACKL, B. SCHWARZ, N. SALAK, E. DEUSCH, W. PAJK, H. J. WOLF, B. RIEDMANN AND W. HASIBEDER

Summary

Haemorrhage is associated with intestinal mucosal hypoxia and impaired gut barrier function. Dopamine increases oxygen delivery to the intestinal mucosa and may thus counteract haemorrhage-induced mucosal hypoxia. Jejunal mucosal tissue oxygen tension (mucosal $P\mathrm{o}_2$) and jejunal oxygen saturation of mucosal microvascular haemoglobin (mucosal $\mathrm{Hb}_{\mathrm{O}_2}$) were measured in 14 anaesthetized pigs. Seven animals served as controls (group C) and seven received continuous infusion of dopamine 16 μg kg^{-1} min^{-1} (group D) while 45% of blood volume was removed in three equal increments. Resuscitation was performed using shed blood and fluid. Mean arterial pressure and systemic oxygen delivery decreased significantly during haemorrhage and returned to baseline after resuscitation in both groups. Mucosal $P\mathrm{o}_2$ decreased from 4.4 to 1.7 kPa after haemorrhage ($P<0.01$) and further to 1.5 kPa after resuscitation ($P<0.01$) in group C whereas group D showed an increase from 3.9 to 5.9 kPa after the start of the dopamine infusion ($P<0.05$), but no significant difference from baseline after haemorrhage (2.3 kPa) (ns) or resuscitation (3.1 kPa) (ns). Mucosal $\mathrm{Hb}_{\mathrm{O}_2}$ decreased from 52 to 32% after haemorrhage ($P<0.05$) and increased to near baseline (37%) (ns) after resuscitation in group C whereas group D showed no significant changes from baseline (54 %) throughout the experiment. Comparison between groups showed higher mucosal $P\mathrm{o}_2$ and $\mathrm{Hb}_{\mathrm{O}_2}$ values for group D animals after the start of the dopamine infusion ($P<0.05$ each), after the first two steps of haemorrhage ($P<0.01$ each) and after resuscitation ($P<0.05$ each). We conclude that i.v. dopamine 16 μg kg^{-1} min^{-1} improved tissue oxygenation of the small intestinal mucosa during moderate haemorrhage and subsequent resuscitation. (*Br. J. Anaesth.* 1997; **79**: 357–362).

Key words
Sympathetic nervous system, dopamine. Complications, haemorrhage. Gastrointestinal tract, mucosal oxygenation. Pig.

The intestinal vascular response to haemorrhage is characterized by mesenteric arterial vasoconstriction and redistribution of blood flow from the muscularis towards the mucosal layer of the intestinal wall.[1] Despite this autoregulatory escape phenomenon, tissue hypoxia during haemorrhage occurs primarily within the mucosal layer of the intestine.[2] Mucosal tissue hypoxia has been implicated as an important mechanism contributing to haemorrhage-induced mucosal tissue injury, increased mucosal permeability and microbial translocation.[3,4] Dopamine is a known intestinal vasodilator[5] and therefore may counteract haemorrhage-induced intestinal mucosal hypoxia. Recent studies suggest that dopamine may specifically increase mucosal blood flow and tissue oxygenation by redistributing blood flow from the intestinal muscularis and serosa towards mucosa.[6,7] Dopamine has been reported to attenuate the concomitant decrease in mucosal villus blood flow after endotoxin-induced mucosal vasoconstriction,[8] and to increase mucosal tissue $P\mathrm{o}_2$.[9] However, the efficacy of dopamine in preserving intestinal mucosal oxygenation during haemorrhage has never been investigated.

The purpose of this study was to examine the effects of dopamine on small intestinal mucosal oxygenation during stepwise haemorrhage and subsequent resuscitation. Tissue oxygenation was assessed directly using two different and independent measuring techniques: Clark-type surface oxygen electrodes for evaluation of mucosal tissue oxygen tension and tissue reflectance spectrophotometry for determination of oxygen saturation of mucosal microvascular haemoglobin. A pig model was chosen because of the anatomical and physiological similarity of the digestive and cardiovascular systems of swine and humans.[10]

Materials and methods

ANIMAL PREPARATION

The study was approved by the Federal Ministry of Science and Research. Fourteen domestic pigs (33–41 kg) were fasted overnight, but had free access

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REINHARD GERMANN, MD, MARKUS HAISJACKL, MD, BIRGIT SCHWARZ, MD, NATALIE SALAK, MD, ENGELBERT DEUSCH, MD, WERNER PAJK, WALTER HASIBEDER, MD (Department of Anaesthesia and General Intensive Care Medicine); HANS JOACHIM WOLF, MD (Institute for Histology), BERNHARD RIEDMANN, MD (First Department of Surgery); University of Innsbruck, Anichstraße 35, A-6020 Innsbruck, Austria. Accepted for publication. April 3, 1997

to water. The animals were anaesthetized with ketamine hydrochloride 20 mg kg^{-1} i.m., the trachea intubated orally and the lungs ventilated mechanically with a positive end-expiratory pressure of 5 cm H_2O. Tidal volume and ventilatory frequency were adjusted to maintain Pa_{CO_2} at 4.7–5.7 kPa. FI_{O_2} was adjusted to maintain Pa_{O_2} at 13.3–16.0 kPa. Anaesthesia was maintained by continuous infusion of fentanyl 20 µg kg^{-1} h^{-1} and midazolam 0.8 mg kg^{-1} h^{-1}. Neuromuscular block was produced by bolus injections of vecuronium 0.15 mg kg^{-1}.

After induction of anaesthesia the right carotid artery was cannulated for measurement of systemic mean arterial pressure and for blood sampling. A balloon-tip thermodilution pulmonary artery catheter (Baxter Edwards Critical-Care, Irvine, CA, USA) was inserted via the right internal jugular vein for measuring cardiac output and pulmonary artery occlusion pressure, and for mixed venous blood sampling. A separate 14-gauge catheter was inserted via the right internal jugular vein for infusion of dopamine. An 8.5-French gauge catheter was inserted into the left internal jugular vein for withdrawal of 45% of calculated blood volume in three steps.

A midline laparotomy was performed and a small part of the jejunal mucosa exposed by an antimesenteric enterotomy. The boundary of the mucosa was sutured to the oval opening of a cork plate. The intestine was reintroduced into the abdominal cavity with the exception of the exposed mucosa. The mucosal preparation was covered by a humidified Servo-controlled chamber heated to 37°C.

Animals were given Ringer's lactate and gelatine i.v. to maintain pulmonary artery occlusion pressure at 12–14 mm Hg. The infusion was stopped with the beginning of haemorrhage and resumed with re-transfusion of shed blood.

MEASUREMENT TECHNIQUES

Systemic haemodynamics and blood-gas tensions

Arterial, pulmonary artery and central venous pressures were measured using Statham P10EZ pressure transducers (Spectramed-Statham, Bilthoven, The Netherlands). Cardiac output was measured by the thermodilution method, in triplicate, with 10-ml injections of ice-cooled saline. Arterial and mixed venous blood-gas tensions were measured using an AVL automatic blood-gas analyser (AVL Biomedical Instruments, Graz, Austria) and a haemoximeter (OSM2, Radiometer, Copenhagen, Denmark).

Small intestinal mucosal tissue oxygenation

The methodology has been described previously in detail.[11] Briefly, two Clark-type multiwire surface electrodes (Eschweiler, Kiel, Germany) were positioned on the exposed mucosa to record mucosal tissue oxygen tension (mucosal Po_2). A single electrode consists of eight platinum wires, each 15 µm in diameter, representing eight individual measuring points, and a silver–silver chloride reference electrode. The electrodes were kept in place by small polyvinyl chloride caps surrounded by a transparent thin rubber patch with a diameter of 2 cm. During each set of measurements, mucosal Po_2 was recorded continuously for a period of 150 s at a frequency of 1 Hz. An Erlangen microlightguide spectrophotometer (EMPHO II; BGT, Überlingen, Germany) was used to measure oxygen saturation of the mucosal microvascular haemoglobin (mucosal Hb_{O_2}). The spectrophotometer includes one central illuminating microlightguide surrounded by six detecting microlightguides with a diameter of 250 µm each and a rapidly rotating bandpass interference filter disk for generation of monochromated light within the spectral range of 502–628 nm. This filter disk permits sampling in steps of 2 nm and a sampling rate of 100 spectra s^{-1}. Monochromated light is transmitted to a photomultiplier tube operated at current mode, fed into a current-to-voltage converter, and amplified by a cascade amplifier. The voltage signal is offset compensated, filtered by a low-pass filter, fed into an analogue-to-digital converter and transferred to an IBM compatible computer. The algorithm used to calculate oxygen saturation of microvascular haemoglobin has been validated for intestinal mucosal tissue.[11] The microlightguide array was fixed to the mucosal surface in a manner identical to that used for the Po_2 electrode. At each measuring time, 1024 values of mucosal Hb_{O_2} were recorded at a frequency of 7 Hz.

EXPERIMENTAL PROCEDURE (FIG. 1)

After surgical preparation, pigs were allowed to stabilize for 120 min. Pulmonary artery occlusion pressure was maintained at 12–14 mm Hg by infusion of Ringer's lactate and gelatine. At the end

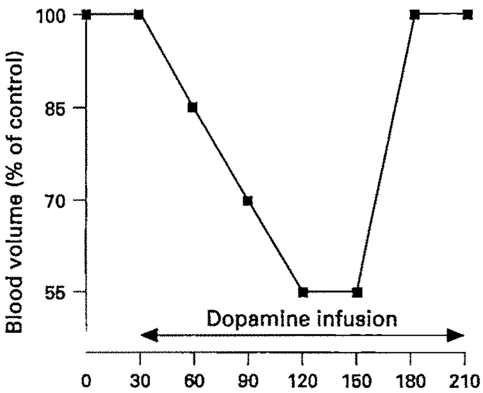

Figure 1 Experimental design. After baseline measurements of haemodynamic and tissue oxygenation variables (t=0 min), seven animals served as controls (group C) and seven animals received continuous infusion of dopamine 16 µg kg^{-1} min^{-1} (group D). In both groups 45% of calculated blood volume was removed in three equal steps. Resuscitation was performed using re-transfusion of shed blood and infusion of fluid in order to restore pulmonary artery occlusion pressure to baseline. Measurements of systemic haemodynamic variables and intestinal mucosal tissue oxygenation were made at 30-min intervals.

of the stabilization period, baseline measurements of haemodynamic state, blood-gas tensions and intestinal tissue oxygenation were performed ($t=0$ min). At this time, animals were allocated randomly to one of two experimental groups: group C ($n=7$) served as controls, whereas group D ($n=7$) received continuous i.v. infusion of dopamine 16 μg kg^{-1} min^{-1} with a concentration of saline 2 mg ml^{-1} (Leopold Inc., Graz, Austria), begining after baseline measurements and continued throughout the experimental period. After a set of measurements at $t=30$ min, infusion of Ringer's lactate and gelatine was stopped in both groups and 45% of calculated blood volume was removed in three equal steps. Measurements of the above variables were repeated after every bleeding step (at $t=60$ min, $t=90$ min and $t=120$ min). After measurements at $t=150$ min, shed blood was re-transfused and infusion of Ringer's lactate and gelatine was resumed in order to restore pulmonary artery occlusion pressure to baseline. Two final measurements were performed at $t=180$ min and $t=210$ min.

At the end of the experiment, animals were killed with a central venous bolus injection of potassium chloride 40 mmol.

STATISTICAL ANALYSIS

Results are expressed as mean (SEM). Comparison between baseline values was made using the unpaired *t* test. Overall effects within and between groups were evaluated by repeated measurement analysis of variance (ANOVA). In the case of significant differences, further comparisons were made with paired *t* tests (within-group to baseline) and unpaired *t* tests (between groups at individual times). $P \leq 0.05$ was considered significant. The Bonferroni–Holm procedure was used for correction of multiple comparisons.

Results

There were no significant differences in baseline systemic variables between group C (no dopamine) and group D (dopamine) (table 1).

Mean arterial pressure, pulmonary artery occlusion pressure and systemic oxygen delivery decreased significantly during stepwise bleeding and returned to baseline after resuscitation in both groups. Systemic oxygen consumption and arterial pH did not change significantly over time in either group. Except for a significant increase after resuscitation in group C animals, arterial packed cell volume (PCV) remained unchanged.

JEJUNAL MUCOSAL TISSUE OXYGENATION (FIGS 2, 3)

There were no significant differences in baseline mucosal tissue oxygen tension (mucosal Po_2; fig. 2) and oxygen saturation of mucosal microvascular haemoglobin (mucosal Hb_{O_2}; fig. 3) between the two groups.

In group C animals, mucosal Po_2 decreased progressively from 4.39 (0.37) kPa at baseline to 1.75 (0.20) kPa after stepwise bleeding ($t=150$ min) ($P<0.01$) and further to 1.45 (0.47) kPa after resuscitation with shed blood and fluid ($t=210$ min) ($P<0.01$). In group D animals, mucosal Po_2 increased from 3.85 (0.48) to 5.87 (0.52) kPa after starting dopamine ($t=30$ min) ($P<0.05$), decreased to 2.32 (0.45) kPa after bleeding ($t=150$ min)—which was not significantly different from baseline—and increased again to 3.09 (0.57) kPa after resuscitation ($t=210$ min). Comparison between groups showed that mucosal Po_2 was higher in group D animals after the start of the dopamine infusion ($t=30$ min) ($P<0.05$), after the first two steps of bleeding ($t=60$ and 90 min) ($P<0.01$ each) and after resuscitation ($t=210$ min) ($P<0.05$).

Table 1 Changes in systemic variables in animals treated without (group C) and with dopamine (group D) during stepwise bleeding ($t=60$, 90, 120 min), after bleeding ($t=150$ min) and after resuscitation ($t=180$, 210 min). Baseline is $t=0$ min. Dopamine infusion was started after baseline in group D animals. MAP=Mean arterial pressure; PAOP=pulmonary artery occlusion pressure; Do_2=systemic oxygen delivery; $\dot{V}o_2$=systemic oxygen consumption; pH_a=arterial pH; PCV=packed cell volume. Values are mean (SEM). *$P<0.05$, **$P<0.01$ *vs* baseline (paired *t* test)

	Time (min)							
	0	30	60	90	120	150	180	210
MAP (mm Hg)								
Group C	111 (7)	111 (7)	105 (6)	76 (3)**	63 (4)**	69 (4)**	120 (3)	117 (4)
Group D	105 (4)	107 (4)	95 (6)	74 (9)**	59 (8)**	65 (7)**	114 (8)	119 (7)
PAOP (mm Hg)								
Group C	13.9 (3)	13.4 (0.4)	11.3 (0.5)**	9.6 (0.4)**	9 (0.7)**	8 (0.2)**	14.4 (0.6)	12.4 (0.7)
Group D	13.9 (1)	12 (0.8)	9.1 (0.7)**	7.9 (0.8)**	6.9 (0.9)**	7.4 (0.8)**	12.9 (0.5)	12 (0.9)
Do_2 (ml kg^{-1} min^{-1})								
Group C	20.9 (1.8)	20.7 (2.2)	16.2 (1.5)	10.8 (0.4)**	8.8 (0.6)**	9.9 (0.5)**	15.2 (1.7)	15.6 (1.1)
Group D	21.2 (2.5)	24.1 (1.9)	20.3 (1.3)	13.4 (1.6)*	11.2 (0.9)**	10.8 (0.9)**	21.3 (1)	19.9 (1.5)
$\dot{V}o_2$ (ml kg^{-1} min^{-1})								
Group C	6 (0.8)	6.1 (0.8)	5.5 (0.7)	4.6 (0.4)	4.1 (0.4)	4.8 (0 5)	5 (0.3)	4.8 (0.4)
Group D	6.5 (0.8)	6.6 (0.7)	6.2 (0.6)	5.7 (0.5)	5.6 (0.3)	5.4 (0.3)	6.1 (0.4)	5.7 (0.4)
pH_a								
Group C	7.46 (0.02)	7.46 (0.01)	7.46 (0.01)	7.46 (0.01)	7.43 (0.01)	7.42 (0.01)	7.43 (0.02)	7.47 (0.01)
Group D	7.48 (0.01)	7.47 (0.01)	7.46 (0.01)	7.45 (0.02)	7.41 (0.02)	7.39 (0.03)	7.39 (0.04)	7.45 (0.03)
PCV (%)								
Group C	22.6 (1.1)	24 (1.2)	23.2 (1.2)	22.5 (1.1)	22.7 (1.2)	22.7 (1.4)	23.6 (1.4)	25.6 (1)**
Group D	25.1 (1.8)	27.1 (1.4)	27.3 (1.1)	25.5 (0.9)	25.4 (0.9)	25.8 (0.8)	27.8 (1.1)	28.3 (0 8)

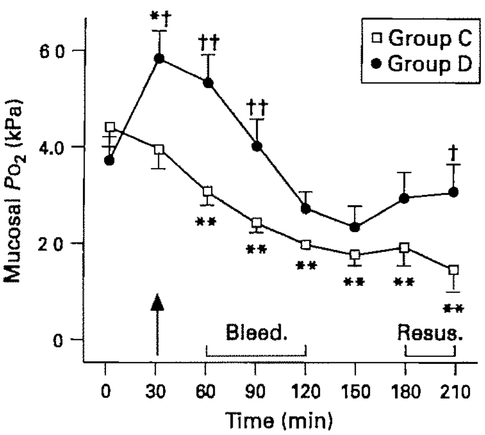

Figure 2 Changes in mucosal tissue $P\text{O}_2$ in animals treated without (group C) and with (group D) dopamine, during and after stepwise bleeding (Bleed.) and resuscitation (Resus.). Baseline is t=0 min. Dopamine infusion was started after baseline in group D animals (arrow). Values are mean (SEM). *$P<0.05$, **$P<0.01$ *vs* baseline (paired t test); †$P<0.05$, ††$P<0.05$ *vs* group C (unpaired t test).

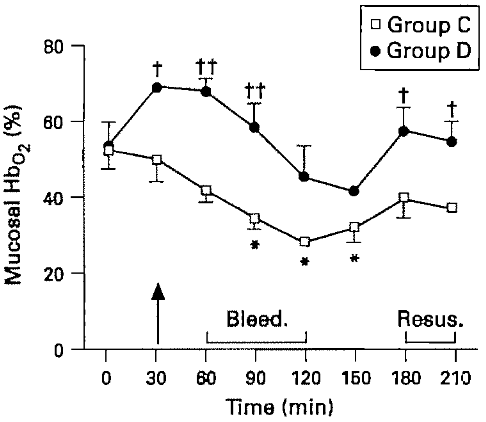

Figure 3 Changes in oxygen saturation of mucosal microvascular haemoglobin (mucosal Hb_{O_2}) in animals treated without (group C) and with (group D) dopamine during and after stepwise bleeding (Bleed.) and resuscitation (Resus.). Baseline is t=0 min. Dopamine infusion was started after baseline in group D animals (arrow). Values are mean (SEM). *$P<0.05$ *vs* baseline (paired t test); †$P<0.05$, ††$P<0.05$ *vs* group C (unpaired t test).

In group C animals, mucosal Hb_{O_2} decreased from 52 (5) % to 32 (4) % after haemorrhage (t=150 min) ($P<0.05$) and increased to 37 (2) % after resuscitation (t=210 min) (ns). In group D animals, mucosal Hb_{O_2} was never significantly different from baseline, despite an increase from 54 (6) % to 69 (1) % after the start of dopamine (t=30 min), a decrease to 50 (8) % after haemorrhage (t=150 min) and an increase to 55 (5) % after resuscitation (t=210 min). Comparison between groups showed that mucosal Hb_{O_2} was higher in group D animals after the start of the dopamine infusion (t=30 min) ($P<0.05$), after the first two steps of haemorrhage (t=60 and 90 min, $P<0.01$ each) and after resuscitation (t=180 and 210 min, $P<0.05$ each).

Discussion

HAEMORRHAGE AND SMALL INTESTINAL MUCOSAL TISSUE OXYGENATION

In this study stepwise loss of 45% total blood volume progressively reduced small intestinal mucosal tissue oxygenation in the pig (figs 2, 3). Spectrophotometrically determined mucosal Hb_{O_2} reflects oxygen delivery to the mucosal and, to a lesser extent, the submucosal layer of the intestinal wall[12] and has been shown to be related linearly to changes in mucosal blood flow during bleeding.[13] The 39% reduction observed at the end of the bleeding period in this study is similar in magnitude to declines in mucosal Hb_{O_2} and blood flow in comparable haemorrhage models.[14 15] This is the first study to measure mucosal tissue $P\text{O}_2$ within the small intestine during bleeding. Clark-type surface $P\text{O}_2$ electrodes appear to be specifically suitable for monitoring tissue oxygenation of the small intestine, as their catchment volume is limited to the villus tip area.[16] The villus tip is thought to be preferentially susceptible to tissue hypoxia during haemorrhage or other intestinal low-flow conditions,[4] because tissue $P\text{O}_2$ is considerably lower at the villus tip than at the base, already under resting conditions.[17] This $P\text{O}_2$ gradient is enlarged during reductions in mucosal blood flow.[18] Thus critically low tissue $P\text{O}_2$ values first appear at the villus tip. In these experiments, mucosal $P\text{O}_2$ was reduced by 60% of baseline values after haemorrhage and thus was more pronounced than total mucosal oxygen delivery, as measured by mucosal Hb_{O_2}. In contrast with mucosal Hb_{O_2}, mucosal $P\text{O}_2$ did not recover after resuscitation with shed blood and fluid even though arterial pressure and systemic oxygen delivery returned to prehaemorrhagic values (table 1). Therefore, decreased tissue oxygenation persisted mainly within the villus tip area. This finding is in accordance with the morphological observation of villus tip injury after resuscitated haemorrhage.[3]

DOPAMINE AND MUCOSAL TISSUE OXYGENATION

Infusion of dopamine 16 μg kg^{-1} min^{-1} increased mucosal $P\text{O}_2$ and mucosal Hb_{O_2} above baseline values in this pig model, although only changes in mucosal $P\text{O}_2$ were statistically significant (group D animals, figs 2, 3; t=30 min). This observation is in agreement with previous findings where i.v. infusion of dopamine 2–32 μg kg^{-1} min^{-1} enhanced jejunal mucosal $P\text{O}_2$ and Hb_{O_2} in a dose-related manner but did not change jejunal serosal $P\text{O}_2$.[7] Similarly, in cats, dopamine 10–25 μg kg^{-1} min^{-1} increased jejunal blood flow to the mucosa and submucosa, whereas muscularis and serosal blood flow decreased slightly.[6] In contrast, intra-arterial infusion of dopamine 0.1 and 0.5 μg kg^{-1} min^{-1} into the superior mesenteric artery of dogs has been reported to increase total mesenteric blood flow but to decrease mucosal blood flow as measured by radioiodine absorption from the gut lumen.[19] However, the results obtained were only descriptive, as the sample size of two dogs at each dose did not allow statistical analysis. Thus the majority of experimental data suggests that dopamine selectively improves intestinal mucosal blood flow and tissue oxygenation. Mucosal vasodilatation seems to be mediated mainly by stimulation of postsynaptic vascular DA_1 receptors, as blockade of these receptors by specific antagonists prevents vasodilatation to a considerable extent,[20] and DA_1 specific agonists such as fenoldopam increase mucosal P_{O_2} which is similar to dopamine.[21]

Dopamine-mediated mucosal vasodilatation maintained tissue oxygenation near baseline after withdrawal of 30% of total blood volume in this study (figs 2, 3; $t=60$ and 90 min), demonstrating that dopamine was effective in improving tissue oxygenation during moderate levels of haemorrhage. However, during and after the last step of bleeding, where volume of shed blood was increased to 45% of total blood volume, mucosal P_{O_2} and Hb_{O_2} decreased to similar absolute values in both groups and a significant difference between the groups was no longer observed (figs 2, 3; $t=120$ and 150 min). The intestinal vasoconstrictor response induced by haemorrhage is mediated by stimulation of the sympathoadrenal and renin–angiotensin system and is largely dependent on volume of shed blood.[22] Hence, when blood loss exceeds 30% of total blood volume, dopamine is no longer effective in competing with the pronounced vasoconstrictor stimulus. A marked difference between the two groups was observed after resuscitation (figs 2, 3; $t=180$ and 210 min); while mucosal tissue P_{O_2} remained significantly decreased in group C animals and reached minimum values at the end of the observation period, recovery to near baseline was observed in group D animals. Mucosal Hb_{O_2} was also significantly higher in group D than in group C animals after resuscitation. Therefore, intestinal mucosal tissue oxygenation could be restored completely in dopamine-treated animals, whereas depressed tissue oxygenation persisted in controls, especially within the villus tip area. It should be noted that dopamine may have improved mucosal blood flow and tissue oxygenation by increasing perfusion pressure within the superior mesenteric circulation in addition to regional vasodilatation. However, this latter mechanism seems unlikely to have occurred in these experiments as arterial pressure did not differ between groups (table 1).

CLINICAL RELEVANCE AND LIMITATIONS OF THE STUDY

Haemorrhage-induced intestinal mucosal hypoxia has been shown to contribute to impaired gut barrier function in experimental models, as seen by increased mucosal permeability, bacterial translocation and mucosal injury.[3] As alterations in gut barrier function may contribute to the pathophysiological processes leading to multiple organ failure and death in severely ill patients,[23] prevention of intestinal mucosal hypoxia seems to be a valuable therapeutic aim in the clinical setting. Our data suggest that dopamine 16 $\mu g\ kg^{-1}\ min^{-1}$ may be useful in improving intestinal mucosal tissue oxygenation during haemorrhage and subsequent resuscitation. A previous study in the same model demonstrated that an equal dose of dopamine produced a more than four-fold increase in intestinal mucosal tissue P_{O_2} after endotoxin-mediated mucosal vasoconstriction.[9] However, these results should be extrapolated to humans and especially to critically ill patients with great caution. Responses of the peripheral vasculature to dopamine have been shown to vary between different mammals.[24] Studies in dogs suggest that the vasodilator effect of dopamine within the superior mesenteric circulation can be overridden by concurrent stimulation of α adrenoceptors at doses higher than 10 $\mu g\ kg^{-1}\ min^{-1}$.[5 25] Yet, this vasoconstrictor effect in dogs is not representative of other mammals, such as pigs, cats and rabbits, where vasodilatation persists at i.v. doses of 20,[26] 25[6] and 50 $\mu g\ kg^{-1}\ min^{-1}$.[24] In humans, the mesenteric vasoconstrictor threshold is still unknown. Clinical evaluation of whether or not dopamine is suitable to treat intestinal mucosal hypoxia could be facilitated by monitoring techniques measuring mucosal tissue oxygenation. At present the only clinical technique that is thought to provide an estimate of gastrointestinal mucosal perfusion or tissue oxygenation is gastric tonometry,[27] which permits pH calculation of gastric mucosal cells (pH_i). Only one study has examined the effects of dopamine on pH_i in hypotensive patients with hyperdynamic sepsis.[28] That study conflicts with ours as a decrease in pH_i was observed, despite an increase in arterial pressure and systemic oxygen delivery during infusion of dopamine. Although a high mean infusion rate of dopamine 26 $\mu g\ kg^{-1}\ min^{-1}$ was used, it is unlikely that this effect on pH_i was caused by α adrenoceptor-mediated mucosal vasoconstriction, as treatment with noradrenaline, a more potent α adrenoceptor agonist, in the same study caused an increase in pH_i. A different explanation is based on observations that dopaminergic receptors may not be distributed uniformly within the gastrointestinal tract. The proximal portion of isolated human gastroepiploic arteries responded to dopamine with α adrenoceptor-mediated vasoconstriction, whereas the distal epiploic branches responded with DA_1 receptor-mediated vasodilatation.[29] Similarly, after infusion of dopamine 25 $\mu g\ kg^{-1}\ min^{-1}$, vascular resistance in the superior mesenteric artery decreased by 50%, whereas it did not change in the coeliac artery in the cat.[24] Thus vasodilatation mediated by stimulation of dopaminergic receptors may be limited to specific parts of the gastrointestinal tract, leading to redistribution of blood flow and tissue oxygenation within this organ after infusion of dopamine.

In summary, we observed that dopamine improved mucosal tissue oxygenation of the porcine jejunum during moderate haemorrhage and subsequent resuscitation. At present, extrapolation of these results to humans and especially critically ill patients is limited because it is uncertain if the intestinal mucosal vascular response to dopamine infusion is similar in pigs and humans.

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Effects of magnesium sulphate on the cardiovascular system, coronary circulation and myocardial metabolism in anaesthetized dogs

Y. NAKAIGAWA, S. AKAZAWA, R. SHIMIZU, R. ISHII, S. IKENO, S. INOUE AND R. YAMATO

Summary

We have studied the effects of i.v. bolus doses of magnesium sulphate ($MgSO_4$) 60, 90 and 120 mg kg^{-1} on haemodynamic state, the coronary circulation and myocardial metabolism in nine dogs anaesthetized with pentobarbitone and fentanyl. $MgSO_4$ produced dose-dependent decreases in arterial pressure, heart rate, left ventricular dP/dtmax and left ventricular minute work index (LVMWI) and an increase in the time constant of left ventricular isovolumic relaxation. Stroke volume increased, systemic vascular resistance decreased and cardiac output did not change significantly. $MgSO_4$ produced decreases in coronary perfusion pressure, coronary vascular resistance and myocardial oxygen consumption ($M\dot{V}O_2$). Coronary sinus blood flow, lactate extraction ratio and the ratio of LVMWI to myocardial $M\dot{V}O_2$, that is an index of cardiac efficiency, did not change significantly. This study indicated that the depressant effect of $MgSO_4$ on cardiac function was offset by lowering of peripheral vascular resistance, so that cardiac pump function remained effective, and the almost constant coronary sinus blood flow resulted from the decrease in coronary vascular resistance even at higher doses. (*Br. J. Anaesth.* 1997; **79**: 363–368).

Key words
Hypnotics barbiturate, pentobarbitone. Cardiovascular system, effects. Heart, metabolism. Pharmacology, magnesium sulphate. Dog.

Magnesium sulphate has been used for decades in the management of eclampsia[1 2] and pregnancy-induced hypertension.[3 4] Recent reports on magnesium have emphasized its role in deficiency syndromes,[5–7] including cardiac arrhythmias.[8 9 10] The therapeutic importance and physiological roles of magnesium have been summarized by Iseri and French,[11] and an extensive review on clinical experiences has been published by James.[12]

The evidence for cardiac depression by clinically useful concentrations of hypermagnesaemia is less clear, despite its wide clinical use. Some authors have demonstrated that there is no evidence of myocardial depression at any concentration of serum magnesium,[13] whereas others have reported that a single injection of magnesium sulphate leads to a decrease in cardiac performance.[14] Although the cardiovascular haemodynamic effects of magnesium sulphate were assessed by some authors in baboons,[13] sheep[15] and humans,[16] there have been few reports on magnesium-induced changes in left ventricular diastolic function. The effects of magnesium sulphate on the coronary circulation and myocardial metabolism have not been studied extensively.

This study was designed to investigate the effects of magnesium sulphate on haemodynamic state, including left ventricular diastolic function, coronary circulation and myocardial metabolism, in open-chest dogs.

Materials and methods

The study was approved by the management committee at Jichi Medical Laboratory of Experimental Medicine, based on the school's Guide for Laboratory Animals, 1993.

Nine mongrel dogs (mean weight 23.5 (range 18–30.5) kg) were anaesthetized with pentobarbitone 30 mg kg^{-1}. After tracheal intubation, the lungs were ventilated with a Harvard pump respirator ($F\text{I}_{O_2}=1.0$). Arterial carbon dioxide tension was maintained at 4.8–5.3 kPa, as assessed by continuous measurement of end-tidal carbon dioxide concentration with a calibrated respiratory gas monitor (Model 5250, Ohmeda, Madison, WI.,USA) and repetitive analyses of arterial blood-gas tensions. Temperature was measured with an oesophageal thermistor and maintained at 36–37 °C using an external heating pad. Anaesthesia was maintained during surgery with fentanyl 20 μg kg^{-1} h^{-1} and 0.5–2.0% sevoflurane in pure oxygen. All animals were paralysed with bolus doses of pancuronium 0.2 mg kg^{-1} followed by small doses as needed.

Heart rate (HR) was monitored by electrocardiography (ECG, lead II), and systolic, diastolic and

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YASUSHI NAKAIGAWA, MD, SATOSHI AKAZAWA, MD, REIJU SHIMIZU, MD, RYOUSUKE ISHII, MD, SHIGEO IKENO, MD, SOICHIRO INOUE, MD, REIKO YAMATO, MD, Department of Anaesthesiology, Jichi Medical School, Tochigi, 329-04, Japan Accepted for publication: April 25, 1997.

Correspondence to Y. N.

mean arterial pressures (SAP, DAP and MAP, respectively) were measured with a micromanometer-tipped catheter (7F 45326, Toyoda, Ltd, Tokyo, Japan) placed via the left femoral artery into the abdominal aorta. A catheter was placed in the abdominal aorta via the right femoral artery for arterial blood sampling. Lactated Ringer's solution was infused at 5–10 ml kg^{-1} h^{-1} into the right femoral vein throughout the experiment.

After median sternotomy, an appropriately sized electromagnetic flow transducer (FB-140T, Nihon Kohden, Ltd, Tokyo, Japan) was placed around the root of the ascending aorta and connected to a flowmeter (MFW2100, Nihon Kohden, Ltd, Tokyo, Japan) for measurement of ascending aortic flow and cardiac output (CO). A micro-tip catheter (8F PC380, Millar, Inc.) was inserted through a stab wound in the apex of the left ventricle for measurements of left ventricular pressure (LVP) and left ventricular end-diastolic pressure (LVEDP). The rate of increase of left ventricular pressure (LVd*P*/d*t*) was obtained with an analogue differentiating circuit incorporated with an analogue-to-digital converter (Contractility Unit 1323, NEC San-ei, Ltd, Tokyo, Japan) and used as an index of left ventricular contractile function. Coronary sinus blood flow (CSBF) was measured by the retrograde thermodilution technique with a catheter (Thermoflow CCS-7U-90A, Webster Labs., Inc.) inserted into the coronary sinus via the right auricle.[17] Cold normal saline as the indicator was infused at 20 ml min^{-1} for 20 s with an infusion pump (SW-367, Sage Inst., Inc.) through the catheter for each measurement of CSBF. A pair of piezoelectric crystals (5 MHz, Sonotek Co., San Diego, CA, USA) were inserted into the subendocardium in the anterior and posterior walls of the left ventricle and connected to an amplifier (amplifier Unit 4105, NEC San-ei., Ltd, Tokyo, Japan) for measurement of left ventricular end-diastolic and end-systolic diameters (LVEDD and LVESD). Fractional shortening (FS) was obtained using the following formula and used as an index of left ventricular contractile function: FS= (LVEDD−LVESD)/LVEDD×100. All variables were recorded continuously on a polygraph (RECTI-HORIZ-8K23, NEC San-ei, Ltd, Tokyo, Japan).

Arterial and coronary sinus blood was sampled simultaneously to measure pH, P_{O_2}, P_{CO_2}, base excess, standard bicarbonate and haemoglobin concentrations (288 Blood Gas System, Ciba Corning), lactate, non-esterified fatty acid (NEFA) and magnesium concentrations. Lactate concentrations were measured using an enzymatic method. Myocardial oxygen consumption ($M\dot{V}O_2$), the ratio of left ventricular minute work index to $M\dot{V}O_2$ (LVMWI/$M\dot{V}O_2$), myocardial oxygen extraction ratio (MO_2ext.), myocardial lactate extraction ratio (MLext.) and myocardial non-esterified fatty acid extraction ratio (MNEFAext.) were calculated. All derived variables and their abbreviations are shown in table 1.

Left ventricular pressure (LVP), LVd*P*/d*t*, LVEDP and ECG signals were fed to a multichannel photographic oscillograph (Visigraph 5137, NEC San-ei Inst., Ltd, Tokyo, Japan) and recorded at a paper speed of 500 mm s^{-1} to obtain the time constant of left ventricular isovolumic relaxation (*T*). *T* was calculated according to the method of Weiss, Frederiksen and Weisfeldt[18] and used as an index of left ventricular relaxation.

At the end of the surgical procedure, sevoflurane was discontinued and fentanyl was infused at a rate of 20 μg kg^{-1} h^{-1}. Approximately 30 min was allowed after withdrawal of sevoflurane for stabilization of haemodynamic variables and baseline values were obtained. All dogs were given a 12.3% solution of magnesium sulphate in a bolus dose of 60, 90 and 120 mg kg^{-1} (0.49, 0.73 and 0.98 ml kg^{-1}, respectively) over 10 s at 20-min intervals consecutively. The ratio of osmolarity of magnesium sulphate to that of saline is 3.0 : 1.0. Haemodynamic measurements and blood sampling were performed 1 min before and after each administration of magnesium sulphate.

All values are presented as mean (SEM). Data were analysed statistically using analysis of variance for repeated measurements (ANOVA). Where appropriate, this was followed by the Scheffe *F* test. A probability of chance occurrence less than 5% ($P<0.05$) was considered statistically significant.

Table 1 Derived variables. BW=Body weight (kg); CO=cardiac output (litre min^{-1}); HR=heart rate (beat min^{-1}); MAP=mean arterial pressure (mm Hg); LVEDP=left ventricular end-diastolic pressure (mm Hg); CVP=central venous pressure (mm Hg); LVEDD=left ventricular end-diastolic diameter (mm); LVESD=left ventricular end-systolic diameter (mm); DAP=diastolic arterial pressure (mm Hg); CSBF=coronary sinus blood flow (ml min^{-1}); (a–cs) DO_2=arterio-coronary sinus oxygen content difference (ml dl^{-1}); Ca_{O_2}=arterial oxygen content (ml dl^{-1}); (a–cs) *D*L=arterio–coronary sinus lactate concentration difference (mg dl^{-1}); La=arterial lactate concentration (mg dl^{-1}); (a–cs) *D*NEFA=arterio- coronary sinus non-esterified fatty acid concentration difference (mEq $litre^{-1}$); NEFAa=arterial non- esterified fatty acid concentration (mEq $litre^{-1}$)

CI	Cardiac index=CO/BW	(litre min^{-1} kg^{-1})
SV	Stroke volume=(CO/HR)×10^3	(ml)
SVI	Stroke volume index=SV/BW	(ml kg^{-1})
LVMWI	Left ventricular minute work index=(MAP–LVEDP)×SVI×HR×0.0136	(g m kg^{-1} min^{-1})
SVR	Systemic vascular resistance=(MAP–CVP)/CO×80	(dyn s cm^{-5})
FS	Fractional shortening=(LVEDD−LVESD)/LVEDD×100	(%)
CPP	Coronary perfusion pressure=DAP–LVEDP	(mmHg)
CVR	Coronary vascular resistance=CPP/CSBF×80	(kdyn s cm^{-5})
$M\dot{V}O_2$	Myocardial oxygen consumption=(a–cs) $DO_{2\times}$CSBF×10^{-2}	(ml min^{-1})
MO_2 ext.	Myocardial oxygen extraction ratio =((a–cs) DO_2/Ca_{O2})×10^2	(%)
MLext.	Myocardial lactate extraction ratio =((a–cs) *D*L/La)×10^2	(%)
MNEFAext.	Myocardial non-esterified fatty acid extraction ratio =((a–cs) *D*NEFA/NEFAa)×10^2	(%)

Table 2 Effects of magnesium sulphate ($MgSO_4$) on cardiovascular state (mean (SEM)). Mg=Serum concentration of magnesium; HR=heart rate; SAP=systolic arterial pressure; DAP=diastolic arterial pressure; MAP=mean arterial pressure; LVEDP=left ventricular end-diastolic pressure; CO=cardiac output; CI=cardiac index; SV=stroke volume; SVI=stroke volume index; LVMWI=left ventricular minute work index; SVR=systemic vascular resistance; LVd*P*/dt_{max}=maximum rate of increase of left ventricular pressure; LVEDD=left ventricular end-diastolic diameter; LVESD=left ventricular end-systolic diameter; FS=fractional shortening; *T*=time constant of fall in isovolumic left ventricular pressure. **P*<0.05, ***P*<0.01 compared with baseline. †*P*<0.05, ††*P*<0.01 compared with $MgSO_4$ 60 mg kg^{-1}

		$MgSO_4$ (mg kg^{-1})		
	Baseline	60	90	120
Mg (mg dl^{-1})	1.3 (0.1)	6.3 (0.3)**	9.7 (0.5)**††	14.4 (0.7)**††
HR (beat min^{-1})	109 (8)	93 (6)	79 (5)**†	69 (4)**††
SAP (mm Hg)	145 (6)	122 (6)**	114 (6)**	97 (7)**††
DAP (mm Hg)	99 (7)	72 (6)**	65 (6)**	53 (6)**††
MAP (mm Hg)	115 (6)	89 (6)**	81 (6)**	69 (6)**††
LVEDP (mm Hg)	3.9 (0.5)	4.1 (0.5)	4.7 (0.6)	4.5 (0.6)
CO (litre min^{-1})	2.2 (0.1)	2.4 (0.1)	2.3 (0.2)	2.0 (0.1)
CI (litre min^{-1} kg^{-1})	0.10 (0.01)	0.11 (0.01)	0.10 (0.01)	0.09 (0.01)
SV (ml)	21.3 (2.3)	26.6 (2.4)	29.3 (2.9)*	29.1 (3.0)*
SVI (ml kg^{-1})	0.98 (0.16)	1.21 (0.17)*	1.32 (0.19)**	1.29 (0.18)**
LVMWI (g m kg^{-1} min^{-1})	146 (14)	121 (12)	104 (14)*	74 (9)**††
SVR (dyn s cm^{-5})	4376 (506)	3076 (335)*	3058 (372)**	2833 (303)**
LVd*P*/dt_{max} (mm Hg s^{-1})	2468 (210)	1974 (194)**	1721 (206)**	1320 (188)**††
LVEDD (mm)	36.0 (6.8)	35.7 (6.6)	36.3 (6.6)	36.6 (6.5)
LVESD (mm)	42.8 (6.2)	42.9 (6.2)	43.8 (6.0)	43.3 (5.5)
FS (%)	19.1 (4.2)	20.3 (3.6)	20.0 (4.0)	20.0 (3.6)
T (ms)	48.0 (4.4)	55.6 (5.1)*	62.3 (5.8)**	67.5 (5.2)**††

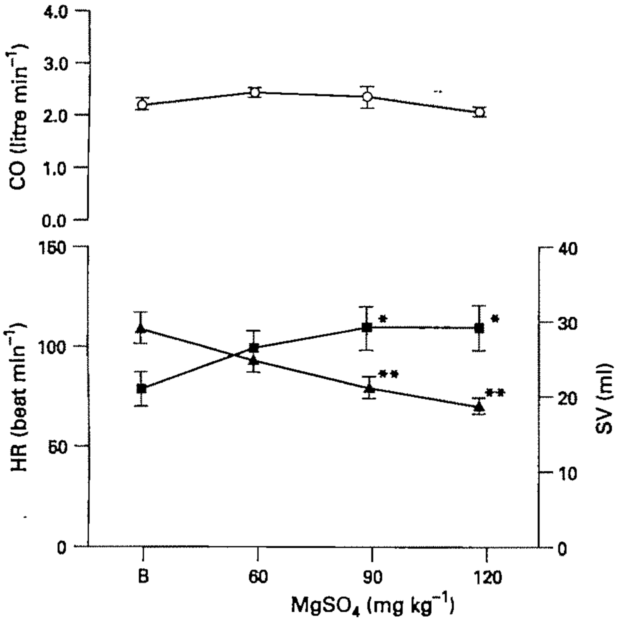

Figure 1 Changes in cardiac output (CO) (○), heart rate (HR) (▲) and stroke volume (SV) (■) (mean, SEM) after administration of magnesium sulphate ($MgSO_4$). **P*<0.05, ***P*<0.01 compared with baseline (B).

Results

Serum concentrations of magnesium 1 min after each bolus administration and the effects on haemodynamic state are shown in table 2. Haemodynamic variables decreased within the first minute and gradually returned to near baseline values after 20 min. Serum concentrations of magnesium before and after administration of magnesium sulphate of 60, 90 and 120 mg kg^{-1} were 1.3 (0.1), 6.3 (0.3), 9.7 (0.5) and 14.4 (0.7) mg dl^{-1}, respectively. Magnesium sulphate produced dose-dependent

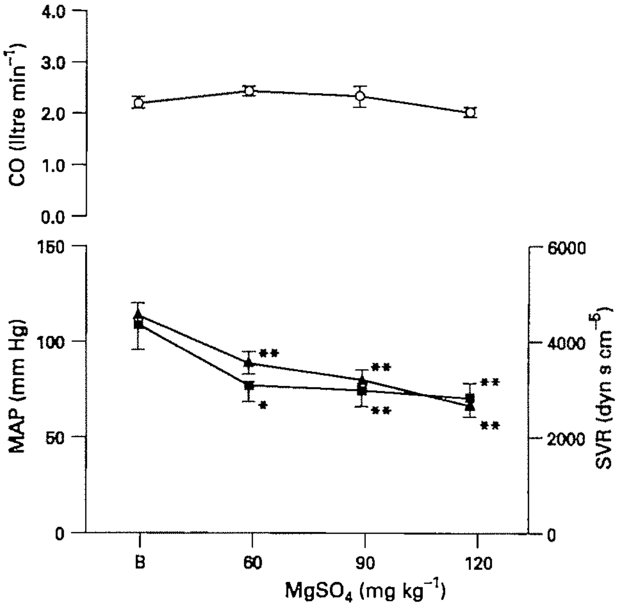

Figure 2 Changes in cardiac output (CO) (○), mean arterial pressure (MAP) (▲) and systemic vascular resistance (SVR) (■) (mean, SEM) after administration of magnesium sulphate ($MgSO_4$). **P*<0.05, ***P*<0.01 compared with baseline (B).

Table 3 Effects of magnesium sulphate ($MgSO_4$) on electrocardiogram (mean (SEM)). SCL=Sinus cycle length, QTc=QT interval corrected for heart rate (Bazett's formula). **P*<0.05, ***P*<0.01 compared with baseline. †*P*<0.05, ††*P*<0.01 compared with $MgSO_4$ 60 mg kg^{-1}

		$MgSO_4$ (mg kg^{-1})		
	Baseline	60	90	120
SCL (ms)	571 (40)	664 (42)**	783 (56)**††	895 (53)**††
PQ (ms)	124 (6)	148 (6)	168 (8)**†	184 (8)**††
QRS (ms)	79 (3)	80 (2)	84 (2)**	86 (2)**
QT (ms)	429 (25)	481 (26)**††	513 (27)**††	563 (29)**††
QTc (ms)	570 (26)	592 (27)*	584 (29)	599 (29)*

Table 4 Effects of magnesium sulphate ($MgSO_4$) on coronary circulation and myocardial metabolism (mean (SEM)). CPP=Coronary perfusion pressure; CSBF=coronary sinus blood flow; CO=cardiac output; CVR=coronary vascular resistance; $M\dot{V}O_2$=myocardial oxygen consumption; Mo_2ext.=myocardial oxygen extraction ratio; MLext.=myocardial lactate extraction ratio; MNEFAext.=myocardial non-esterified fatty acid extraction ratio; LVMWI=left ventricular minute work index. *$P<0.05$, **$P<0.01$ compared with baseline. †$P<0.05$, ††$P<0.01$ compared with $MgSO_4$ 60 mg kg^{-1}

		$MgSO_4$ (mg kg^{-1})		
	Baseline	60	90	120
CPP (mm Hg)	90 (8)	64 (7)**	57 (7)**	40 (4)**††
CSBF (ml min^{-1})	91.7 (4.4)	112.5 (12.1)	106.9 (12.9)	89.2 (15.7)
CSBF/CO (%)	4.4 (0.3)	5.0 (0.6)	5.4 (0.8)	4.7 (0.8)
CVR (kdyn s cm^{-5})	81 (10)	49 (6)**	47 (7)**	42 (6)**
$M\dot{V}O_2$ (ml min^{-1})	5.4 (0.3)	4.8 (0.6)	3.9 (0.6)	2.7 (0.3)**††
Mo_2ext. (%)	44.3 (2.1)	36.6 (4.4)	32.7 (4.1)*	31.6 (4.4)*
MLext. (%)	42.1 (4.2)	37.1 (4.5)	33.8 (4.6)	31.7 (7 9)
MNEFAext. (%)	20.4 (2.3)	24.1 (5.2)	27.0 (7.1)	34.9 (9.5)
LVMWI/$M\dot{V}O_2$ (g m kg^{-1} $litre^{-1}$)	24.0 (2.3)	24.0 (3.7)	23.1 (2.4)	22.3 (3.7)

decreases in HR, SAP, DAP, MAP, LVMWI and LVd*P*/d*t* max ($P<0.01$). Stroke volume increased significantly but cardiac output did not change significantly (fig. 1). The near constant CO may have been brought about by the decrease in systemic vascular resistance (SVR) (fig. 2). LVEDD, LVESD and FS did not change significantly. *T* increased in a dose-dependent manner, indicating a decrease in left ventricular diastolic function.

The effects of magnesium sulphate on the electrocardiogram are shown in table 3. Magnesium sulphate increased sinus cycle length, PQ and QT intervals dose-dependently ($P<0.01$). QRS duration and corrected QT interval (QTc) increased significantly, but not dose-dependently. P wave, ST segment and T wave configurations did not change significantly. Magnesium sulphate did not produce arrhythmia.

The effects of magnesium sulphate on the coronary circulation and myocardial metabolism are shown in table 4. Magnesium sulphate produced dose-dependent decreases in coronary perfusion pressure (CPP) and $M\dot{V}O_2$ ($P<0.01$). Coronary vascular resistance (CVR) and Mo_2ext. ratio decreased, but not dose-dependently. Any significant changes in CSBF, the ratio of CSBF to CO, MLext. ratio, MNEFAext. ratio and LVMWI/$M\dot{V}O_2$ were not observed at each dose of magnesium sulphate.

Discussion

The major findings of this study were that magnesium sulphate, in a dose-dependent manner, lowered systemic vascular resistance, arterial pressure and heart rate, while cardiac output was well maintained. Cardiac work, derived from both stroke volume and heart rate, and myocardial oxygen consumption, decreased markedly in parallel with systemic vascular resistance. Magnesium sulphate maintained coronary perfusion and cardiac efficiency even at higher doses.

With an unchanged cardiac output, the decrease in arterial pressures must result from a decrease in systemic vascular resistance, which may be caused mainly by the vasodilator effects of magnesium sulphate that have been demonstrated *in vitro*,[19 20] in intact animals[13 21] and in humans.[15] The cardiovascular effects of magnesium are as follows: (1) inhibition of the normal rhythm or vasomotion (spontaneous mechanical activity) of vascular smooth muscle, (2) depression of the contractile responses to endogenous neurohumoral substances that maintain vascular tone,[22] (3) possibly blockade of sympathetic ganglia[23] and (4) negative inotropism.

In humans, Mroczek, Lee and Davidov[15] reported that infusion of magnesium sulphate resulted in a rapid but transient decrease in arterial pressure in hypertensive patients, whereas normotensive subjects did not demonstrate any appreciable change in arterial pressure. McCubbin and co-workers[24] reported cardiopulmonary arrest caused by acute maternal hypermagnesaemia (35.1 mg dl^{-1}). In animals, transient[16] and marked[13 25] hypotension has been reported. This transient hypotension may be explained partially by rapid clearance of magnesium from plasma through the kidney. James, Cork and Dennett[13] demonstrated the difficulties of maintaining high serum magnesium concentrations in the presence of normal renal function. They administered in the baboon a loading dose of 60 mg kg^{-1} over 1 min and then infused continuously 12.5 mg min^{-1} for at least 5 min. The infusion rate was then increased to 25 mg min^{-1} and by 25 mg min^{-1} every 5 min up to a maximum of 200 mg min^{-1}. The maximum serum magnesium concentration attained was only 9.4 mmol $litre^{-1}$. Dandavino and colleagues[16] observed that rapid administration of magnesium sulphate produced hypotension but a more gradual administration did not produce hypotension. In our study, magnesium sulphate at bolus doses of 60, 90 and 120 mg kg^{-1} administered every 20 min produced a dose-dependent decrease in arterial pressure. This decrease in arterial pressure corresponded to increases in serum concentrations of magnesium.

Magnesium sulphate is known to have a negative inotropic action and cause myocardial depression and cardiac arrest in massive doses.[24] In this study, magnesium sulphate produced a dose-dependent decrease in LVd*P*/d*t*max. Although the decrease in LVd*P*/d*t*max can be explained partially by the decrease in heart rate,[26] this indicates that magnesium sulphate exerted a dose-dependent negative inotropic action in the whole animal. Left ventricular pump function, however, was well compensated by the increase in stroke volume caused by the lowering of peripheral vascular resistance. In fact, magnesium sulphate 60 and 90 mg kg^{-1} produced a significant increase in stroke volume despite a marked decrease in LVd*P*/d*t*max. Cardiac output also was maintained well at a high dose of 120 mg kg^{-1}. The profound decrease in heart rate may be the main effect of magnesium sulphate, with the heart compensating by a Starling effect to increase stroke volume appreciably. This finding is consistent with previous reports.[3 13 27] James, Cork and Dennett[13] demonstrated that cardiac output was maintained at control values, at concentrations of serum magnesium greater than 5 mmol $litre^{-1}$. Cotton, Gonik and Dorman[3] and Mroczek, Lee and Davidov[15] also demonstrated that magnesium sulphate produced an increase in cardiac output despite significant myocardial depression. These findings and ours suggest that the direct myocardial depressant effect with magnesium may be compensated by decreased afterload, resulting in the maintenance of cardiac function as a pump. No significant change in fractional shortening as an index of left ventricular systolic function during ejection phase could be attributed to the decrease in afterload.

Some authors[16 25] have reported that tachycardia occurred during administration of magnesium sulphate, whereas others[13] have reported that bradycardia was seen. In our study, magnesium sulphate produced a dose-dependent decrease in heart rate and prolongation of PQ and QTc intervals. The degree and rate of increase of blood magnesium concentration may partially explain the different findings observed among these studies. At a low serum concentration of magnesium, hypotension may produce tachycardia through the baroreflex pathway, whereas at a high concentration bradycardia may be brought about by both indirect and direct inhibitory effects of magnesium on the sinoatrial node. As for indirect inhibitory effects, Stanbury[23] found that magnesium induces a short-lived blockade of the sympathetic ganglia and prevents the stimulating effects of potassium and acetylcholine on the superior cervical ganglion in anaesthetized cats. As for direct inhibitory effect, Opthof and colleagues[28] demonstrated that magnesium itself decreased the rate of diastolic depolarization of the pacemaker cells in the sinus node.

In this study, magnesium sulphate did not produce any arrhythmias or conduction disorders at serum concentrations of 6.3 (0.3) to 14.4 (0.7) mg dl^{-1}, although it produced a dose-dependent decrease in heart rate and prolongation of PQ, QRS and QTc intervals. This finding is consistent with our earlier study[29] except for QTc interval. The difference of basal anaesthesia may be associated with the different results of QTc interval.

Although the effects of magnesium sulphate on systemic haemodynamic state and myocardial contractility have been described in other studies,[13 15 16] the effect on ventricular diastolic function *in vivo* or *in vitro* remains unexplored. In this study, the effect of magnesium sulphate on left ventricular relaxing function was investigated by the time constant of left ventricular isovolumic relaxation (*T*). The shorter the *T* value, the better the relaxing function of the left ventricle, and vice versa.[18] Magnesium sulphate produced a dose-dependent increase in *T* in this study. Therefore, magnesium may depress left ventricular relaxing function. Because *T* tends to increase with a decrease in heart rate and depressed systolic fibre shortening,[18] the decrease in *T* observed here appeared to be related not only to decreased left ventricular relaxing function but also to decreased heart rate and depressed systolic fibre shortening.

The effects of magnesium sulphate on the coronary circulation and myocardial metabolism have not been studied extensively. This study demonstrated that magnesium sulphate did not change coronary sinus blood flow remarkably despite a decrease in coronary perfusion pressure. This suggests that magnesium sulphate may have a coronary vasodilating effect. A dose-dependent decrease in $M\dot{V}O_2$ appeared to parallel the decreased external work of the heart, because LVMWI/$M\dot{V}O_2$ did not change significantly. The decrease in LVMWI is thought to be caused mainly by reduction in arterial pressure. Lactate production was not observed throughout this study. Therefore, magnesium sulphate may maintain an appropriate oxygen supply-and-demand relation in the myocardium and may exert no major adverse effects on cardiac function as a pump.

The findings of this study could be related to basal anaesthesia because of an acute open-chest canine preparation under general anaesthesia. Priebe demonstrated an anaesthetic technique comprising pentobarbitone, with fentanyl maintaining a stable, global haemodynamic state over a prolonged period.[30] Cox[31] demonstrated that haemodynamic variables returned to control levels within 15 min after pentobarbitone 30 mg kg^{-1} i.v. in dogs, although heart rate remained increased from the control value of 85 beat min^{-1} to 132 beat min^{-1} even after 60 min. In this study, however, a heart rate of 125 (5) beat min^{-1} immediately after administration of pentobarbitone decreased to a baseline value of 109 (8) beat min^{-1} immediately before initiation of measurements.

The osmolarity of magnesium sulphate solutions used could not produce any transient cardiovascular effects because the volumes were small and osmolarity might be lowered by the circulating blood of the dogs.

Magnesium sulphate competes with calcium at the cell membrane and is regarded in many clinical situations as a physiological calcium blocker. This concept may be supported by the facts that magnesium sulphate (1) exerted a mild consistent, dose-dependent hypotensive effect, (2) preserved cardiac pump and coronary sinus blood flow despite a decrease in coronary perfusion pressure, (3) produced negative inotropic effect, (4) decreased myocardial oxygen consumption and (5) did not produce arrhythmia. These effects are thought to be beneficial for patients with ischaemic heart disease.

In future, magnesium will be used more widely in many medical situations, including anaesthetic practice as a physiological calcium blocker.

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REVIEW ARTICLE

Pain after laparoscopy

J. I. ALEXANDER

Laparoscopy (Greek λαπαρα—flank, or λαπαροσ—soft; σκοπηιν—to look) involves insufflation of the abdomen by gas or other fluid so that the endoscope (usually 6–10 mm in diameter) can view the intra-abdominal contents without being in direct contact with the viscera or tissues. Surgical procedures can be carried out by instruments introduced through one or more additional ports. Laparoscopy therefore defines the surgical approach and is associated with pain which is additional to that caused by intra-abdominal trauma. Nevertheless, pain which occurs after this procedure is significantly less and shorter than that caused by the same surgical procedure made possible by laparotomy.[7,45,50,65,90] The total costs of the procedure are less[32] and the long-term morbidity is less than when performed by laparotomy.[88] The reduction in both pain and loss of function has made possible earlier discharge from hospital,[64] provided that control of residual pain is not by drugs which also prevent discharge because of nausea, ileus or reduction of consciousness and autonomous function.[70,99] Early discharge also reduces the safety of powerful analgesics and makes difficult monitoring and adequate treatment of pain after laparoscopy.

Timing and pattern of pain after laparoscopy

Pain may occur in the upper abdomen, lower abdomen, back or shoulders. It may be transient or persist for at least 3 days.[26,79] Shoulder pain may occur in as many as 63%[78] or as few as 35% of patients.[26] The incidence is not altered if suxamethonium is used to facilitate tracheal intubation.[98] The greatest incidence of pain is in the upper abdomen.[26] Reporting of pain (at any site) is greatest after operation, decreases to a low level within 24 h, but increases to a second or even a third peak later.[2,4,26] Joris and colleagues[46] reported that after laparoscopic cholecystectomy, visceral pain predominates in the first 24 h but subsides from a peak soon after operation, whereas shoulder pain, minor on the first day, increases and becomes significant on the following day.

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Mechanism of pain after laparoscopy

This has been reviewed by Schoeffler, Diemunsch and Fourgeaud.[81] Rapid distension of the peritoneum may be associated with tearing of blood vessels, traumatic traction of the nerves and release of inflammatory mediators. The prolonged presence of shoulder tip pain[26,45,78] suggests excitation of the phrenic nerve. This pain is present often after laparotomy[65] and both laparotomy and laparoscopy are associated with persistent pneumoperitoneum, sometimes for 3 days. There is a statistically significant correlation between the width of the gas bubble and pain score,[42] and this pain can be reduced by aspiration of the gas under the diaphragm,[78] by "active aspiration", that is repeated suction and manipulation,[30] by the use of a gas drain [2] or by application of local anaesthesia under the diaphragm under direct vision[71,73] or through a sub-phrenic catheter.[34] Peritoneal inflammation or the presence of gas is probably also the origin of the upper abdominal pain after lower abdominal surgery or after diagnostic laparoscopy. This also can persist for at least 3 days.[26] The use of nitrous oxide instead of carbon dioxide for peritoneal insufflation may not be responsible for the intra-abdominal explosions reported,[41] but it alters insignificantly the incidence and severity of postoperative pain or nausea and vomiting.[43,55] Comyn[18] reported that peritoneal biopsy performed 2–3 days after laparoscopy showed peritoneal inflammation and neuronal rupture, and there was a linear inverse relationship between abdominal compliance at the time of laparoscopy and severity of postoperative pain. Suxamethonium may be used to facilitate intubation and its use can be associated with pain across the shoulders, but its avoidance is not associated with a reduction of pain in the shoulders.[98]

PAIN AFTER LAPAROSCOPIC STERILIZATION

Laparoscopic sterilization is probably the most common operation by laparoscopy in the UK. It is more painful than diagnostic laparoscopy.[29,39] Davis and Millar[23] showed that laparoscopic sterilization pain was worse than that after diagnostic

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J. I. ALEXANDER, MB, BS, FRCA, Sir Humphry Davy Department of Anaesthesia, Bristol Royal Infirmary, Bristol BS2 8HW

laparoscopy for the first 4 h after operation but was not significantly greater after hospital discharge on the same day as surgery. Analgesia tends to be given more readily during studies of pain or analgesics than at other times so that the incidence of pain after laparoscopic tubal occlusion is difficult to judge from published studies. In some placebo-controlled studies of postoperative analgesics, some of the patients in the control groups did not receive additional analgesia (see Larsen and Jensen[52]). Nearly all, however, had received some form of intraoperative analgesia.

The three methods of tubal ligation commonly used are diathermy, ring or loop occlusion and clips (e.g. Hulka or Filshie). There is considerable difference in the amount of lower abdominal pain between the methods. Chi and Cole[14] found more pain both during the procedure (under local anaesthesia) and after operation when rings were used than when spring-loaded clips were used. Dobbs and colleagues[26] found that the incidence and severity of lower abdominal pain were significantly higher after ring sterilization than after Hulka clip sterilization and that the pain after clip sterilization did not differ significantly from that after diagnostic laparoscopy . The greatest difference was in lower abdominal pain in the first 6 h after operation. Huang and colleagues[40] found that, under local anaesthesia, tubal diathermy caused more pain than Falope rings but that after 4 h the pain after rings exceeded that of diathermy. Lawson, Cole and Templeton[53] (and Leggat and Barr[54] retrospectively) found that Falope rings were associated with administration of more analgesics than electrocoagulation (diathermy). Comfort and colleagues[17] found that the pain of clips exceeded that after diathermy and others also noted the similarity in character and distribution of colicky pain at and after sterilization with that of dysmenorrhoea.[40]

Pain relief

LOCAL ANAESTHESIA

Pain after diagnostic laparoscopy can be reduced significantly by a bilateral rectus sheath block, performed above the umbilicus with approximately 15 ml of 0.25% bupivacaine on each side.[86]

The pain that follows tubal ligation can be lessened by application of local anaesthetic directly to the fallopian tube or by injection into the mesosalpinx[1 72 85] at operation. This has been shown to have an effect after rings or bands, but also after fulguration or even when applied at the same time, as a gel, as the Filshie clip.[6 48 60 62 75] McKenzie and colleagues[61] reported that 1% etidocaine, when applied to the fallopian tubes from the uterus to the fimbriae, was superior to 0.75% bupivacaine. Its use led to reduced postoperative use of morphine and fewer admissions to hospital overnight.

The total pain of laparoscopy can be reduced by application of local anaesthesia under the diaphragm under direct vision,[73] through an irrigation device[38] or through a sub-phrenic catheter.[34] Shoulder pain after pelvic peritonoscopy can be reduced by either lignocaine or bupivacaine i.p.,[57] and the addition of adrenaline[71] permitted a large volume to be used without approaching systemic toxicity.[87] Conversely, local anaesthetics administered i.p. seem to be ineffective for either visceral or shoulder pain after laparoscopic cholecystectomy[46 77 80] but these studies did not document a head-down tilt to bathe the tissues supplied by the phrenic nerve. However, Schulte-Steinberg and colleagues[82] found that a single injection of interpleural 0.25% bupivacaine 30 ml, but not interpleural morphine 1.5 mg, morphine 1.0 mg i.p. or 0.25% bupivacaine 20 ml i.p., significantly reduced the global pain after laparoscopic cholecystectomy for 6 h in a randomized, double-blind, saline-controlled study of 110 patients. The intraperitoneal drugs were sprayed under pressure over the gallbladder bed and the diaphragmatic surface of the liver. This did not greatly affect the pain perceived in the shoulders. Of patients who received a peritoneal injection, seven of 50 complained of shoulder pain at 6 h, and 24 complained at 24 h. Of those who received interpleural injections, seven of 60 reported shoulder pain at 6 h, and 23 at 24 h. Those reporting shoulder pain were distributed evenly between the treatment and control groups. However, Chundrigar and colleagues,[15] using 20 ml of 0.25% bupivacaine directly onto the gallbladder bed, reported significant pain relief.

Pelvic laparoscopy can be performed under spinal anaesthesia alone, either intrathecally[84] or extradurally,[31] and, in an uncontrolled cohort, caudal extradural anaesthesia provided effective pain relief in children after laparoscopic transperitoneal herniorrhaphy.[91]

NON-STEROIDAL ANTI-INFLAMMATORY DRUGS

The amount of pelvic pain after tubal manipulation or tubal ligation may be related to concentrations of prostaglandins. Prostaglandin concentrations are known to increase with dysmenorrhoea. Prostaglandin $PGF_{2\alpha}$ is found in the human oviduct at 10 times the concentration found in plasma. Its localization changes at the time of ovulation. $PGF_{2\alpha}$ is found mainly in the isthmus and correlates with motility of this region, whereas PGE_1 is found in the ampulla.[13 74 94] The human ovarian follicle contains both PGE_2 and $PGF_{2\alpha}$ in critical amounts. Laparoscopic tubal manipulation and ligation release prostaglandins, which may increase the frequency of nociceptive impulses and cause pain. This pain may therefore be amenable to prostaglandin synthase inhibitors. Rarely however, is lower abdominal pain assessed separately from upper abdominal, chest or shoulder pain. Even when it is, pain scores and re-medication may be used for the global pain experience.[2 19 98]

EFFICACY OF NON-STEROIDAL ANTI-INFLAMMATORY DRUGS (NSAID)

The prospective, randomized, controlled comparisons of NSAID with placebo which showed that NSAID were superior to placebo in reducing pain or reducing

Table 1 Randomized controlled studies in which NSAID showed more efficacy than placebo after laparoscopy

Reference	NSAID	No. of subjects	Time of dministration	Route	Opioid given to all subjects	Procedure	Pain intensity	Additional analgesic requirements	Time to first pain or analgesic assessment (h)
Davie and colleagues[22]	Fenoprofen 200 mg	45	Postop prn	Oral	No	Not stated	Reduced	Reduced	
Brodie and Casper[8]	Indomethacin 100 mg	42	Post-induction	Rectal	Yes	Sterilization with rings	Not stated	Reduced	0.5
Huang and colleagues[40]	Paracetamol 1300 mg	50	1 h preop.	Oral	No	Sterilization with diathermy or rings under LA	Reduced	Not stated	1.5
DeLucia and White[24]	Ketorolac 30 mg	50	Preop.	I.m.	Yes	Not stated	Reduced	Reduced	1
DeLucia and White[24]	Ketorolac 60 mg	50	Preop.	I.m.	Yes	Not stated	Reduced	Reduced	1
Comfort and colleagues[17]	Naproxen 550 mg	47	1 h preop.	Oral	Yes	Sterilization with clips or diathermy	Reduced	Reduced	1.5
Gillberg and colleagues[33]	Diclofenac 50 mg	46	I h preop.	Rectal	Yes	Diagnostic/ sterilization	Reduced	Reduced	0.5
Hovorka and colleagues[39]	Diclofenac 100 mg	99	Post-induction	I.v.	Yes	Diagnostic	Not stated	Reduced	0.5
Liu and colleagues[56]	Ketorolac 60 mg	60	10–20 min preop.	I.v	Yes	Cholecystectomy	Reduced	Reduced	2
Van Ee and colleagues[93]	Naproxen 500 mg	58	I h preop.	Rectal	No	Diagnostic	Reduced	Not used	1.5
Green and colleagues[37]	Ketorolac 60 mg	70	30 min pre-recovery	I v.	Yes	Diagnostic	Reduced	Reduced	0.5
Wilson and colleagues[95]	Diclofenac 75 mg	49	Post-induction	I.m.	Yes	Cholecystectomy	Reduced	No significant diffifference	
Dunn and colleagues[28]	Naproxen 1000 mg	74	90 min preop.	Oral	Yes	Sterilization with clips	Similar	Reduced	2

Table 2 Randomized controlled studies in which NSAID failed to show more effect than placebo

Reference	NSAID	No. of subjects	Time of administration	Route	Opioid added to both groups	Procedure	Pain intensity of NSAID group	Additional analgesic requirements	Time to pain or analgesic assessment (h)
Mclennan and colleagues[63]	Indomethacin 100 mg	95	1 h preop.	Rectal	Yes	Sterilization with clips/rings	Less but $P>0.05$	Similar; $P=0.3$	1.5
Edwards and colleagues[29]	Diclofenac 75 mg	40	Post-induction	I.m.	No	Diagnostic	Less but $P>0.05$	Similar	0.5
Edwards and colleagues[29]	Diclofenac 75 mg	40	Post-induction	I.m.	No	Sterilization with clip	Less but $P>0.05$	Similar	0.5
Crocker and Paech[19]	Indomethacin 100 mg	50	2 h preop.	Rectal	Yes	Sterilization with clips	Less but $P=0.07$	Less but $P=0.07$	2.5
Hovorka and colleagues[39]	Diclofenac 100 mg	70	Post-induction	I.v.	Yes	Sterilization	Not stated	Similar	0.5
Shapiro and Duffy[83]	Ketorolac 30 mg	40	Post-induction	I.m.	Yes	Sterilization with clips	Less but $P>0.05$	Less but $P>0.05$	0.5
Windsor and colleagues[96]	Tenoxicam 20 mg	67	At induction	I.v.	Yes	Diagnostic	Less but $P>0.15$	Less but $P>0.15$	0.5

the requirement for additional analgesic after laparoscopy are shown in table 1. Those which showed no significant benefit of NSAID compared with placebo are shown in table 2.

COMPARISON OF NSAID WITH OTHER ANALGESICS FOR THE PAIN AFTER PELVIC LAPAROSCOPY

Randomized, controlled comparisons of NSAID with other analgesics are shown in table 3. NSAID have been compared with paracetamol, codeine, oxycodone, fentanyl, morphine, pethidine, dexmedetomidine and dezocine.

Comparison with paracetamol[40] showed that meclofenamate was more effective in reducing the pain of tubal ligation during and after local anaesthesia, although both drugs were insufficient in most cases. However, both drugs were given 1 h before operation and peak concentrations of oral paracetamol were achieved at approximately 1 h in plasma and at 4 h in CSF,[5] so that maximal analgesia would not have been achieved at the time of surgery.

Dexmedetomidine was effective in reducing the need for other analgesia but was distinguished by increased somnolence and bradycardia, such that 33% of such subjects required atropine.[3] Dezocine was associated with a higher incidence of nausea or vomiting (60%) than either ketorolac or fentanyl, and most of the dezocine subjects required antiemetic therapy.[25] In a comparison of zomepirac 100 mg with codeine 60 mg[27] for the pain of sterilization with diathermy or rings, there was little difference in pain intensity or additional opioid requirements. Zomepirac has since been withdrawn because of the incidence of NSAID-related side effects. Ketorolac 30 mg i.m. has been compared with pethidine 100 mg i.m. after induction of anaesthesia.[11] Duration of operation was not stated, but at 30 min after operation those who had received pethidine had only marginally less pain, at 1 h there was no difference, and at 4 h after operation the

Table 3 Randomised controlled comparisons of effects of NSAID and other analgesics on pain after laparoscopy

Reference	NSAID	No of subjects	Time of administration	Route	Opioid given to all subjects	Procedure	Comparator	Pain intensity	Additional opioid requirements
Davie and colleagues[22]	Fenoprofen 200 mg	43	Postop when required	Oral	No	Not stated	Morphine 8 mg i.m.	Increased	Similar
Dunn and colleagues[27]	Zomepirac 100 mg	48	30 min preop	Oral	No	Sterilization with diathermy/rings	Codeine 60 mg orally	Similar	Similar
Huang and colleagues[40]	Meclofenamate 100 mg	50	1 h preop.	Oral	No	Sterilization with diathermy/rings	Paracetamol 1300 mg orally	Reduced	Not stated
Huang and colleagues[40]	Meclofenamate 200 mg	50	1 h preop	Oral	No	Sterilization with diathermy/rings	Meclofenamate 100 mg	Similar	Not stated
Rosenblum and colleagues[79]	Ibuprofen 800 mg	30	1 h preop.	Oral	No	Diagnostic laparoscopy	Fentanyl 75 μg	Similar	Similar
Aho and colleagues[3]	Diclofenac 250 μg kg^{-1}	48	Postop when required	I.v.	No	Sterilization with clips	Oxycodone 60 μg kg^{-1} i.v.	Increased	Increased
Aho and colleagues[3]	Diclofenac 250 μg kg^{-1}	48	Postop. when required	I.v.	No	Sterilization with clips	Dexmedetomidine 0.4 μg kg^{-1}	Increased	Increased
Grace and colleagues[35]	Diclofenac 75 mg	80	Pre-induction	I.m	No	Sterilization with rings	Fentanyl 100 μg	Increased/ decreased	See text
Ding and White[25]	Ketorolac 60 mg	88	Pre-induction	I.v.	Yes	Not stated	Fentanyl 100 μg	Reduced	Reduced
Ding and White[25]	Ketorolac 60 mg	92	Pre-induction	I.v.	Yes	Not stated	Dezocine 6 mg	Similar	Similar
Cade and Kakulas[11]	Ketorolac 30 mg	60	Post-induction	I.m.	Yes	Sterilization	Pethidine 100 mg	Reduced	Reduced
Lysak and colleagues[58]	Ketorolac 60 mg	56	30 min preop	I.m	Yes	Not stated	Fentanyl 100 μg	Reduced	Similar
Lysak and colleagues[58]	Piroxicam 40 mg	55	90 min preop.	Oral	Yes	Not stated	Fentanyl 100 μg	Reduced	Similar

ketorolac group had significantly less pain than the pethidine group.

Both of these groups were given fentanyl during operation and this technique was used in a large minority of the comparisons.[11 25 35 58] When fentanyl was given during operation, either as a single bolus or as cardiovascular changes indicated, and sufficient time elapsed before assessment of analgesia, ketorolac[25 58] reduced postoperative pain more than fentanyl alone. When NSAID were the sole analgesics for sterilization, they were less effective than morphine[22] or oxycodone.[3] For diagnostic laparoscopy without sterilization, ibuprofen and fentanyl were equally effective.[79] In a double-blind, double-dummy study of 80 patients undergoing sterilization with Falope rings, diclofenac i.m. was compared with fentanyl i.v.[35] At approximately 40 min after administration of diclofenac and 30 min after fentanyl, less pain was associated with fentanyl. However, 30 min later, in those requesting additional analgesia, the fentanyl group reported more pain. Perhaps more significantly, most pain scores in the first 2 h after operation were unsatisfactorily high (authors' own comment) and the scores of those who requested additional analgesia were not always higher than those who did not. The time to the first analgesic, when given, was also similar in both groups.

These results suggest that NSAID in usual therapeutic doses are more effective than paracetamol. They also suggest that analgesia associated with NSAID was broadly similar to that of short-acting opioids such as pethidine or fentanyl provided that the assessment is made around the peak action of the NSAID or at the end of the duration of action of the opioid. The combination of an NSAID and a short-acting opioid is more effective in intensity and duration than the short-acting opioid alone. However, comparisons of diclofenac with oxycodone and fenoprofen with morphine showed that the longer-acting opioid was clinically significantly more effective.

NSAID AND POST-LAPAROSCOPIC CHOLECYSTECTOMY PAIN

Wilson and colleagues[95] investigated diclofenac 75 mg i.m. at induction of anaesthesia compared with placebo. Intraoperative fentanyl 3 μg kg^{-1}, with supplements as required, was used in all patients. A second dose of the drug was given after 12 h and morphine was given as required. Pain was scored on a visual analogue scale at 4, 24 and 48 h after operation. In the diclofenac group, pain was significantly less at 4 h and there was a lower consumption of morphine (ns).

Liu and colleagues[56] gave ketorolac 30 mg, 15 min before induction, another 30 mg after intubation and 60 mg 4 h after operation, and compared ventilatory, recovery and analgesic effects with saline. Duration of anaesthesia was approximately 2 h. Significantly lower pain scores were recorded in the ketorolac group. One-third of the ketorolac group and two-thirds of the saline group required additional post-operative analgesia. There was no significant difference in anxiety, sedation or nausea between the two groups. There was also no difference in the severity of ventilatory dysfunction.

The undisputed success of NSAID in this operation relative to pelvic laparoscopy may be because the pain was relatively more dependent on inflammatory mediators, because the operation was longer and more intraoperative analgesics were given, or because there was a longer time from administration to assessment of the NSAID.

FAILURE OF NSAID TO PROVIDE MORE PAIN RELIEF THAN PLACEBO

There appears to be wide variation in efficacy of NSAID on pain after laparoscopy. Some randomized, double-blind, controlled studies showed insignificant effects, although none suggested that NSAID were less effective than placebo. This lack of efficacy is contrary to the numerous studies which demonstrate a convincing analgesic effect or opioid-sparing effect of NSAID for the pain of more invasive surgery[12 20 69 92] in which pain scores were used and opioid use was measured by patient-controlled analgesic administration.

MacLennan and colleagues[63] showed that there is an insignificant reduction in the numbers of patients requiring pethidine, and in the amount of pethidine given, in those who received an indomethacin suppository 1 h before operation compared with those who had a dummy suppository. Almost 100 patients took part, but the method of determining the analgesic efficacy may not have been sensitive enough. The recovery room nurses, who were unaware of the preoperative medication, gave either pethidine or a combination of paracetamol and codeine for postoperative pain at their discretion and at apparently different doses. Only pethidine consumption was recorded and pain was not scored. The method was unable to detect a difference in pain levels caused by clip or ring sterilization.

Edwards and colleagues[29] also demonstrated a lower pain score after laparoscopic sterilization at 20 min and 1 h and 20 min after diclofenac i.m. (compared with no injection) and, although the median of one pain score was more than 3 SEM less than the other, the difference between the two groups of 20 patients was not significant.

Significantly reduced opioid requirements after diclofenac 75 mg for diagnostic laparoscopy but not for laparoscopic sterilization have been reported,[39] although even in the latter procedure, the diclofenac group required slightly less fentanyl and paracetamol after operation. Perhaps a lack of difference or lack of sensitivity can be found in the method of pain titration and in the timing of assessment. Pain was not scored. Analgesics in large aliquots (fentanyl 50 μg i.v. or paracetamol 0.5 g rectally) were given "according to clinical judgement". Observer scores of pain were usually less than those of the patient and there would be reluctance to use additional large doses for small increases in pain. Diclofenac was given after induction of anaesthesia and approximately 27 min before the end of anaesthesia, possibly 30 min before the first assessment of pain and analgesic requirements. However, Green and colleagues were also able to detect a differential benefit for NSAID after diagnostic laparoscopy[37] but not after laparoscopic sterilization.[36]

Prados and Blaylock[76] found no benefit of ketorolac 30 or 60 mg given 15–20 min before the end of surgery, as tested by the use of patient administered and controlled fentanyl. Ketorolac was given i.m. and titration of analgesic to pain in the recovery room might be expected to be achieved without the influence of ketorolac but the amount of analgesic self-administered during admission was only marginally reduced in the ketorolac 60 mg group and not in the ketorolac 30 mg group.

Windsor and co-workers[96] found a non-significant improvement in pain score and a reduction in the number of rescue doses of fentanyl after tenoxicam i.v. at induction of anaesthesia. Pain and pain rescue were measured over 24 h. Tenoxicam is slow in analgesic onset and the peak action may be too late to treat pain susceptible to NSAID.

Although the provision of pain relief in the recovery period is variable and the efficacy of analgesics is dependent on patient expression of

Table 4 Assessment of pain and analgesic requirement in randomized controlled comparisons of NSAID and placebo

Reference	Significant effect of NSAID found	Assessment of pain	Assessment of additional analgesic requirement
Mclennan and colleagues[63]	No	Not stated	Amount and type given on discretion of staff
Edwards and colleagues[29]	No	Visual analogue scale (VAS)	Paracetamol, co-proxamol or pethidine given by nurse on request by patient
Edwards and colleagues[29]	No	Visual analogue scale (VAS)	Paracetamol, co-proxamol or pethidine given by nurse on request by patient
Crocker and Paech[19]	No	VASat 0 5, 1 and 3 h	Pethidine 25 mg doses i.v. titrated to patient comfort
Hovorka and colleagues[39]	No	Three-point rating scale assessment by observer	Paracetamol or fentanyl given on observer's judgement of pain
Shapiro and Duffy[83]	No	VAS at 1 and 5 h, peak VAS	Standard protocol: amount recorded
Windsor and colleagues[96]	No	Linear analogue scale and verbal rating scale	Patient request to nurses and pain diary
Davie and colleagues[22]	Yes	Linear analogue scale (LAS) + interview	Patient demand when tolerance exceeded
Brodie and Casper[8]	Yes	Nurse's judgement of analgesic need	Standard protocol of variable analgesia (not double-blind)
Huang and colleagues[40]	Yes	1–5 verbal rating scale	Morphine, meclofenate or paracetamol
Delucia and White[24]	Yes	0–100 las (averaged)	Fentanyl or ketorolac used as rescue analgesia
Delucia and White[24]	Yes	0–100 las (averaged)	Fentanyl or ketorolac used as rescue analgesia
Comfort and colleagues[17]	Yes	VAS at 1 and 2 h	Amount of paracetamol, codeine, pethidine or morphine determined by nurse
Gillberg and colleagues[33]	Yes	10 cm visual analogue scale (VAS)	Pethidine or paracetamol given by nurse
Hovorka and colleagues[39]	Yes	Three-point rating scale assessment by observer	Paracetamol or fentanyl given on observer's judgement of pain
Liu and colleagues[56]	Yes	VAS at 30, 60 90 min postop.	Standard protocol of different analgesics
Van Ee and colleagues[93]	Yes	0–10 numerical rating scale	Paracetamol/naproxen provided on patient request
Green and colleagues[37]	Yes	10 cm visual analogue scale (VAS)	Incremental i v. doses of fentanyl 25 μg
Wilson and colleagues[95]	Yes	10 cm visual analogue scale (VAS)	Morphine 10–15 mg prn
Dunn and colleagues[28]	Yes	Five-point verbal rating scale in recovery and at 2 and 4 h	Mefenamic acid and/or diamorphine on nurse's judgement

demand or nurses' perceptions of pain, even before pain severity is scored, the same objections apply also to those studies in which a significant analgesic effect for NSAID was found (table 4).

NSAID AND SHOULDER PAIN

If the pain perceived in the tips of the shoulders is related to inflammation of the peritoneal reflections supplied by the phrenic nerve, this may also be reduced by anti-inflammatory analgesics.

Although Crocker and Paech[19] found that global pain after laparoscopy and mean requirements for pethidine were less after indomethacin than after placebo ($P=0.09$ or 0.07), shoulder and chest pain was higher in the indomethacin group. Van Ee, Memrika and Van der Linden[93] gave naproxen 500 mg or dummy suppository 1 h before laparoscopy. The control group required more additional analgesics and had higher pain scores than the naproxen group, but the incidence of shoulder tip pain was not different in the two groups. Edwards and colleagues[29] studied women who had undergone either diagnostic laparoscopy or laparoscopic tubal ligation. In each group, patients were given diclofenac 75 mg after induction or no injection. Shoulder pain was noted separately but analgesia was given for total pain. The laparoscopic sterilization group had, on average, significantly more pain than the diagnostic laparoscopy group. Pain scores were lower in the diclofenac group on each assessment but the differences were not significant.

TIMING

The timing of NSAID administration and onset has been reviewed by Moote.[69] There is clearly a latency in onset of analgesic action and a longer delay before peak action. Rosenblum and co-workers[79] showed that the analgesic effect of ibuprofen was apparent only after the patient had left the recovery room. Davie, Slawson and Burt[22] gave oral fenoprofen 200 mg and saline injection when patients complained of pain in a double-blind, double dummy, placebo-controlled study. The assessment was an interview and a 10-cm linear analogue scale. Although those who received fenoprofen had less pain than those who received placebo after 1 h, the difference was not significant until 2 h. Van Ee, Memrika and Van der Linden[93] found naproxen to be more effective than placebo only 30 min after operation, or approximately 2 h after administration of the naproxen suppository.

In the studies which failed to demonstrate a significant analgesic effect of NSAID, the drug was usually given at or after induction of anaesthesia, that is approximately 30 min before rescue analgesia was available for pain in the recovery room, except where indomethacin was administered rectally 1 or 2 h before operation.[19 63] In those in which more than one assessment of pain or analgesic consumption was made, the greatest difference between NSAID and placebo effect was found at 2.5, 4 or 5 h after i.v. or i.m. administration. Similarly, in those studies in which NSAID demonstrated a significant analgesic effect, the greatest effect was found between 2 and 24 h after administration. Dunn, Clark and Jones,[28] using a relatively large dose of the long-acting agent naproxen did not find variation in analgesia with time over the first 24 h.

After oral absorption, there is a delay to peak plasma concentrations of most NSAID of approximately 1–2 h.[89] There may be further delay before peak concentrations at the site of action are reached. For example, regional concentrations of prostanoids within the fallopian tube suggest that surface generation may be less than in the lamina propria, for example. The data sheet for ketorolac (1996–1997) states that "the time to onset of analgesia effect after both intravenous and intramuscular administration is similar and is approximately 30 minutes with maximum analgesia occurring within one to two hours". (The evidence for this statement is difficult to trace in any single study, either by literature search or by direct enquiry to the information service at Syntex (Roche).) Similar data for the peak analgesic effect of i.v. diclofenac are not readily available but the same delay would be expected.[44] Pain assessment and analgesic administration may be occurring before NSAID become effective. It might be argued that NSAID were delayed in onset because they had no effect against prostanoids already synthesized.[69]

Another mechanism may be operative. It is possible that accumulation of the "right-handed" stereoisomer (R enantiomer) may be responsible for the build-up of analgesic effect. The S enantiomer of most (if not all) NSAID shows more anti-inflammatory activity than the R enantiomer, yet the analgesic activity of flurbiprofen for example, is related to both the R and S enantiomers, and prostaglandin inhibition within the brain is significantly inhibited by the pure R enantiomer.[9] Although many NSAID show one-way conversion of R to S enantiomer, via acetyl co-enzyme A for example, this is not universal or (with the exception of ibuprofen) extensive. One-way conversion does not occur with ketorolac in humans[67] but the R form has a half-life approximately twice that of the S form and would accumulate with repeated doses and dominate with time.

NSAID might provide pre-emptive analgesia. A noxious stimulus causes spinal and supraspinal processing, such as "wind-up" at the NMDA channel in the spinal dorsal horn, thereby increasing the throughput of the second-order spinal pain transmission neurones from a given input from the nociceptor through the first-order C fibre nociceptive afferent. If effective analgesia is present before the nocigenic stimulus, there is less wind-up and the total pain experience and total amount of analgesia required is less.[97] However, the pain of the early postoperative period, either by moderate or strong nocigenic stimuli or by mechanical, thermal or noxious stimuli in the presence of inflammation and hyperalgesia, can also cause wind-up.[49] Comparison of the effect of diclofenac given before laparoscopy with that of diclofenac given after did not show any difference in pain or analgesic requirements in the postoperative period.[10] Although allowance was made for the time required for diclofenac to exert its analgesic effect, it did not take into account the nocigenic stimuli in the early postoperative period.

ELIMINATION OF BIAS

In 1983, Dunn and colleagues[27] compared premedication with zomepirac 100 mg, an obsolete NSAID, with codeine 8 mg for prevention of pain after dental extraction and laparoscopy. The assessments of the procedures were considered separately. The study was prospective, randomized, double-blind and double-dummy, and assessments were a 10-cm vertical linear analogue scale and a five-point verbal rating scale. Systemic and local analgesics, with the exception of nitrous oxide, were not used in the general anaesthetic technique. Rescue analgesia was available. Analysis of those who required rescue medication was separated from those who did not. At 5 h after operation, all but one patient in the codeine group had received additional analgesia. Pain scores and rates of re-medication in each group were similar and only by 4 h was there a moderate, but not significant, difference in favour of zomepirac. (Pain scores and rates of re-medication in dental patients suggested that zomepirac was significantly more effective.) The study was not subjected to analysis to estimate the likelihood of demonstrating a difference between the two treatment groups but, in other respects, it achieved a higher standard of objectivity than most that followed. The subsequent study of Brodie and Casper,[8] which has been cited and discussed by almost half of the reports of the randomized studies that followed, was not double-blind (the treatment being dependent on the last digit of the hospital number), nor was pain assessment objective.

Only before the studies of Dunn, Clark and Jones[28] and MacLennan and co-workers[63] was the sample size calculated to achieve an 80% probability of detecting a material difference between the two groups of pain scores or between the numbers requiring analgesia. However, the numbers of patients in the studies which showed NSAID to be superior to placebo were not materially greater than those in studies which failed to show a significant effect.

There are many other studies and reviews or audits of the efficacy of analgesics for pain after laparoscopy, but only randomized controlled studies are included here.

ASSESSMENT OF OUTCOMES (SEE ALSO TABLE 4)

Almost all studies described have used patients' assessments of pain, either with a linear analogue scale, some other form of visual analogue scale, numerical rating scale or with a verbal rating scale. Verbal rating scales show a high level of correlation with linear analogue scores.[51] Occasionally, pain scores were treated not as ordinal data but subjected to parametric analysis and averages compared.[24] This may be defensible.[51] Prados and Blaylock[76] used fentanyl by patient-controlled administration to determine analgesic requirements after outpatient gynaecological surgery which required intubation and ventilation. Unfortunately, the report does not state that all were laparoscopies. However, in one study[8] the method of pain scoring was left to a nurse in recovery and the investigators were not blinded. In another,[63] a large, randomized, double-blind, double-dummy study, with pre-study power analysis, no assessment of pain was made by the patient and two types of rescue analgesia were administered according to patient demand and staff discretion. The study was unable to show any differences between the pain of tubal occlusion by clips and that with rings, as demonstrated by others[14 26]

REVIEW OF REVIEWS

There have been many reviews of NSAID in general, and individually, with regard to their pharmacology, uses and efficacy; few have considered their place in postoperative pain after laparoscopy[16 47 69] and even fewer have adequately considered analgesic requirements in reviews of laparoscopy.[81] The former have described the divergence of opinion of efficacy in comparison with either placebo or with other analgesics. They have commended for consideration the concept of balanced analgesia although there is little evidence for potentiation of quantity or quality of analgesia after laparoscopy and there is evidence of the disadvantage of a greater range of unwanted side effects. Only Schoeffler, Diemunsch and Fourgeaud[81] considered the different types of pain, different mechanisms and some of the various stratagems for overcoming them.

THE PLACE OF NSAID FOR POST-LAPAROSCOPY PAIN

That NSAID are most appropriate for pain after laparoscopy has not been proved. Even the additional pain caused by tubal ligation, possibly mediated by prostaglandins, does not appear to be ideally treated by prostaglandin synthase inhibitors. In one study, pain was relieved better after diagnostic laparoscopy and in another after tubal ligation. Does reduction in opioid use have a clinical advantage? Except in rare cases the need for opioids, especially when given judiciously and frequently, is unlikely to compromise ventilation. The reduced need for opioids is often postulated to reduce nausea and vomiting, ileus and time to readiness for discharge. Yet, usually no difference is found in the times of recovery to the various stages of autonomous function. Nausea and vomiting accompany the pain of both tubal occlusion and dysmenorrhoea[40] and may be unrelated to the use of opioids. Conversely, the antiemetic advantage of propofol for day-case anaesthesia is reduced or lost when papaveretum or morphine is used.[59 66 68] It would seem necessary to administer NSAID 1 h or more before laparoscopy to gain the maximum benefit after operation. At this stage, the accentuated risks of refractory bleeding, hypovolaemia or renal failure are not yet apparent. Bleeding is more difficult to detect and control during laparoscopy than laparotomy. Some studies and other reviews[16] have suggested that the quality of analgesia and patient satisfaction is improved if both NSAID and opioids are used. However, Davie and Gordon[21] have shown that fenoprofen and paracetamol used alone in modest doses were not significantly more effective than placebo, but in combination were significantly superior. This combination would appear to be more suitable for day surgery than the addition of opioids. Despite all the above, it is possible that the measures of pain, usually at rest rather than on movement, and well-being, are too insensitive and that the clinical impression of the nursing staff, based on the summation of many visual and verbal stimuli, should be quantified and tested. It is equally possible that the perception of pain relief by NSAID is an extrapolation from operative models in which NSAID have a more noticeable effect.

Conclusion

Pain which is caused by laparoscopy and laparoscopic surgery is variable in duration, severity and character. The tendency towards reduced hospital stay for laparoscopic procedures leads to failure of recognition and treatment of pain which arises or increases after the first few postoperative hours. Pain which is severe after hospital discharge makes necessary high-cost domiciliary visits and possibly inadequate treatment because of the constraints of the lack of monitoring.

Local anaesthetic techniques, regional or focal, appear more successful for pelvic laparoscopy than for laparoscopic cholecystectomy for example, although interpleural anaesthesia may be effective and safe for unilateral pain. Pain related to stimulation of the phrenic nerve is not easily resolved by extradural anaesthesia without considerable risk or life support.

Non-steroidal anti-inflammatory drugs and paracetamol are not as effective for immediate postoperative pain as are opioids and appear to be ineffective for pain in the shoulders. Their effect in the majority of patients is to reduce the severity of pain or to reduce the need for opioid analgesia. As a sole analgesic, they appear inadequate in most patients. The evidence that the use of NSAID increases recovery or hospital discharge is not consistent. Single intraoperative doses of short-acting opioids such as fentanyl are also inadequate for pain in most cases. However, in many patients, NSAID, given sufficiently early to be effective by the time of waning of the effect of the peroperative opioid, are sufficient to render discomfort tolerable.

Until the various pains are assessed separately and analgesic stratagems are assessed for the different components of the pain experienced, most of these pain-relieving methods will be ineffective because the remaining pain is a sufficient cause of dissatisfaction to maintain demands for rescue analgesia and to increase pain scores. A combination of simple measures, such as evacuating the insufflated gas, application of local anaesthetic gel to the fallopian tubes at the time of clipping, use of a rectus sheath block or local anaesthetic applied to skin and muscle wounds, preoperative use of paracetamol and use of a moderately short-acting intraoperative opioid may reduce the immediate and referred pain effectively and safely. The later inflammatory pain can then be modified with non-opioid drugs such as the anti-inflammatory agents.

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SHORT COMMUNICATIONS

Twitch augmentation and train-of-four fade during onset of neuromuscular block after subclinical doses of suxamethonium

S. Y. KIM, J. S. LEE, S. C. KIM AND W. PARK

Summary

We have studied the train-of-four (TOF) response mechanomyographically during onset of neuromuscular block produced by subclinical doses of suxamethonium in order to follow the augmentation of the first twitch of the TOF (T1) and TOF fade compared with control TOF responses before the drug was given. In the groups given suxamethonium 0.05, 0.1, 0.2 and 0.3 mg kg^{-1}, the increments in T1 after administration of the drug were observed before twitch depression occurred; these were mean 22.3 (SEM 8.1) %, 19.2 (3.3) %, 10.8 (2.0) % and 4.2 (2.2) %, respectively. This effect was more marked with the lower doses ($P<0.05$). The degree of TOF fade was moderate during onset of neuromuscular block and depended on the dose of drug. The results of this study suggest that low doses of suxamethonium produced transient increase in muscle tension and twitch depression with significant TOF fade. We conclude that suxamethonium was associated with presynaptic effects as a consequence of brief stimulation of acetylcholine release followed by progressive diminution at the neuromuscular junction. (*Br. J. Anaesth.* 1997; **79**: 379–381).

Key words
Neuromuscular block, suxamethonium. Neuromuscular block, measurement of response.

It is generally accepted that suxamethonium acts on postjunctional structures causing depolarizing block. This block is the result of opening of cation channels by activation of acetylcholine receptors on the α subunits of the postsynaptic receptor pentamer. However, some investigators have produced evidence that the drug may act on both pre- and postsynaptic receptor sites at the neuromuscular junction.[1] The presynaptic effect of a large amount of acetylcholine is to produce a transient increase in muscle tension because of postsynaptic stimulation followed by depression of neuromuscular transmission as a consequence of inhibition at presynaptic receptors at motor nerve endings.[2] The fade of train-of-four (TOF) response is accepted as a consequence of the presynaptic effect resulting from progressive diminution of the output of acetylcholine.[3] Therefore, we have investigated the simultaneous appearances of these two responses induced by subclinical doses of suxamethonium.

Methods and results

Approval for this study was obtained from the Ethics Committee of Soon Chun Hyang University Hospital. We studied 48 healthy adult patients, ASA I or II, undergoing elective surgery and not suffering from any neuromuscular, renal or hepatic diseases, or receiving any medication which might influence neuromuscular transmission. Patients with a personal or family history of suxamethonium apnoea or malignant hyperthermia were excluded.

Patients were given glycopyrronium 0.2 mg and nalbuphine 10 mg i.m., 1 h before induction of anaesthesia. An i.v. infusion was commenced when the patient arrived in the operating room, and ECG, end-tidal carbon dioxide, oesophageal temperature and arterial pressure were monitored. Surface electrodes (Red Dot, 3M Ag/AgCl) were applied over the ulnar nerve at the wrist and supramaximal TOF stimulation at a frequency of 2 Hz for 2 s delivered by a peripheral nerve stimulator (Innervator, Fisher and Paykel, New Zealand) using 0.2-ms square wave pulses. The trains of stimuli were repeated every 12 s. The twitch response of the thumb adductor was measured mechanomyographically using a cell strain gauge with a 2-kg load (Model No. 505H, RS Component Ltd, UK) with thumb piece modification. Recordings were made on a Gould TA 240 Easy Graf thermal array recorder with a 6600 series transducer.

After thiopentone 4–5 mg kg^{-1} for induction, anaesthesia was maintained with 66% nitrous oxide in oxygen with increments of thiopentone or fentanyl 1 $\mu g\ kg^{-1}$, or both, as required. Ventilation of the lungs was assisted using a face mask, when necessary, to maintain normocapnia. The patient's core temperature was maintained within the normal range. In this study, subclinical doses of suxamethonium were used in order to measure the effect on twitch height and TOF, because it is difficult to obtain TOF responses during the short onset time of

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S. Y. KIM, MD, J. S. LEE, MD, S. C. KIM, MD, W PARK, MD, Department of Anaesthesiology, School of Medicine, Soon Chun Hyang University and Hospital, 58–657 Hannam-Dong, Yongsan-Ku, Seoul 140–210, Korea. Accepted for publication: April 4, 1997.

Correspondence to S. Y K

Table 1 Twitch response data (mean (SEM)) for each subclinical dose of suxamethonium. T1 or T4=First or fourth twitch height of the train-of-four (TOF), TOF ratio=T4/T1 at first TOF response during onset of neuromuscular block after drug administration and at its corresponding twitch height level during recovery. Means with different letters (A, B, C, D) indicate significant differences between groups for each variable ($P<0.05$, Student–Newman–Keuls). $^{*}P<0.05$ compared with recovery (paired Student's *t* test)

	Suxamethonium (mg kg^{-1})					
	0.025	0.05	0.1	0.2	0.3	0.4
Twitch T1 augmentation (%)	—	22.3 (8.1)^{A}	19.2 (3.3)^{A}	10.8 (2.0)^{B}	4.2 (2.2)^{B}	—
Maximum depression (%)	—	5.5 (2.5)^{A}	60.6 (5.2)^{B}	93.4 (1.0)^{C}	98.5 (0.7)^{C}	99.5 (0.5)^{C}
TOF ratio (T4/T1, %) during						
Onset	—	91.7 (1.4)^{*A}	76.5 (1.0)^{*B}	70.3 (1.4)^{*C}	68.7 (1.8)^{*C}	68.6 (1.7)^{*C}
Recovery	—	94.9 (1.1)	91.9 (1.2)	95.4 (1.2)	95.6 (1.9)	92.5 (1.9)

neuromuscular block induced by clinical doses of suxamethonium. After induction of anaesthesia, twitch height of the TOF was allowed to stabilize for at least 10 min and patients were allocated according to randomly selected numbers to receive one of the following subclinical doses of suxamethonium: 0.025, 0.05, 0.1, 0.2, 0.3 or 0.4 mg kg^{-1} i.v. via an indwelling needle at the wrist. Eight patients received each dose.

Neuromuscular recording was continued to measure the following: (1) twitch augmentation (%), defined as the maximum increase in T1 compared with control T1; (2) maximum T1 depression (%), defined as the greatest depression of T1 after injection; and (3) change in TOF ratio (%). This was calculated from the first TOF ratio at the depressed height of T1 during onset after injection and at the corresponding height level of T1 during recovery.

Statistical analysis was performed using SPSS. Results were compared using Kruskal–Wallis one-way analysis of variance (ANOVA) and groups which differed significantly by ANOVA were tested with Student–Newman–Keuls multiple range test to determine differences between groups. The TOF ratio during onset was compared with that during recovery in each group using the paired Student's *t* test. Differences were considered statistically significant at $P<0.05$. Data are reported as mean (SEM).

Twitch augmentations of TOF responses after drug administration were observed before depression of T1 and were greatest for T1 for the four twitch responses of TOF: 22.3 (8.1) %, 19.2 (3.3) %, 10.8 (2.0) % and 4.2 (2.2) % in the groups given suxamethonium 0.05, 0.1, 0.2 and 0.3 mg kg^{-1}, respectively. This effect was more marked with the lower dose ($P<0.05$) (table 1) and was not observed in groups given 0.025 and 0.4 mg kg^{-1}. Partial depression occurred in groups given suxamethonium 0.05, 0.1 and 0.2 mg kg^{-1} and almost complete T1 depression occurred in groups given 0.3 and 0.4 mg kg^{-1}. However, there were no changes in TOF response in the suxamethonium 0.025 mg kg^{-1} group. The degree of TOF fade at the first TOF during onset after drug administration was moderate: 76.5 (1.0) %, 70.3 (1.4) %, 68.7 (1.8) % and 68.6 (1.7) % in the groups given suxamethonium 0.1, 0.2, 0.3 and 0.4 mg kg^{-1}, respectively. TOF fade depended on the dose of drug given. Almost sustained TOF responses occurred during recovery and TOF fade during onset of neuromuscular block was significantly greater than that at the corresponding height of T1 during recovery from neuromuscular block ($P<0.05$) (table 1).

Comment

It is thought that there are at least two populations of presynaptic cholinergic receptors, each subserving different physiological functions: one group is the presynaptic nicotinic receptor which acts as a positive feedback and responds to low concentrations of acetylcholine causing an autofacilitatory effect. This is believed to be mediated partly through its action on synapsin I causing an increase in the immediately available store of acetylcholine increasing the rate of release of acetylcholine after motor nerve activity. The second group is the presynaptic muscarinic receptor which acts as a negative feedback and responds to high concentrations of acetylcholine. Stimulation of these receptors causes reduced release of transmitter in the presence of motor nerve activity. This would explain the response observed experimentally after a large dose of acetylcholine is injected directly into the arterial supply of a muscle; initial powerful contraction is followed by transient neuromuscular block.[2] There is convincing evidence of a physiological mechanism of this type causing an initial positive feedback via autoreceptors on the nerve endings and then negative feedback limiting the effect of the high concentration released.[4] As suxamethonium produces an acetylcholine-like action, it has been proposed that neuromuscular block by this drug is the result of both pre- and postsynaptic sites of action.[5] We have demonstrated that twitch augmentation produced by suxamethonium was apparent in the groups given doses which only partially depress T1 and it was absent in the groups given doses which were either too small to cause block or too large. The results could be explained by proposing that suxamethonium causes brief stimulation of intact presynaptic receptors on motor nerve endings increasing the mobilization of acetylcholine. Any effect is overwhelmed by a large dose which causes complete block. Therefore, it seems likely that suxamethonium, which in some respects resembles acetylcholine, may initially evoke activation of presynaptic cholinergic receptors which augments depolarization of the postsynaptic membrane. Its action then progresses to cause presynaptic depression, block or desensitization.[5]

TOF fade is generally attributed to a presynaptic effect caused by progressive decrease in acetylcholine release from the nerve endings.[6] Presynaptic binding of neuromuscular blocking agents prevents rapid acetylcholine mobilization required to maintain adequate acetylcholine release during rapid stimulation, such as during TOF or tetany. The generally accepted view is that the degree of fade is related to the propensity for presynaptic binding and demonstration of fade can be taken as evidence of presynaptic block of a feedback mechanism.[5] Full depolarizing block induced by suxamethonium is characterized by lack of fade but repeated doses or continuous infusion of drug produces neuromuscular block characterized by tetanic fade, termed phase II block. However, in our study, despite administration of subclinical, small doses of suxamethonium, the TOF response appeared to be associated with approximately 70% TOF fade during onset of block; even during recovery from block, TOF fade did not occur. Otherwise, it is presumed that the moderate fade of TOF response during onset after subclinical doses of suxamethonium results from incomplete block of presynaptic receptors and the sustained TOF response during recovery should result from rapid dissociation from presynaptic sites by enzymatic hydrolysis at the early stage of recovery. However, the different effects observed on TOF fade and T1 depression may be caused by different affinities and rates of binding for pre- and postsynaptic receptors at the neuromuscular junction.[3]

The results of this study suggest that the hypothesis that, although the site of action of suxamethonium is postsynaptic it also has a presynaptic site of action, may be true, but clinically it is masked by large doses.

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British Journal of Anaesthesia 1997; 79: 382–383

Spontaneous movements associated with rocuronium: is pain on injection the cause?

A. BORGEAT AND D. KWIATKOWSKI

Summary

Spontaneous movements are sometimes observed of the arm into which rocuronium is administered. In order to assess a possible relationship between these movements and pain, we injected in 10 awake, ASA I patients, in a double-blind manner, both rocuronium 1 ml (10 mg) and 0.9% NaCl 1 ml (placebo), with a 30-s interval in between. None of the patients receiving placebo complained of pain, but eight of 10 patients reported a strong burning pain during injection of rocuronium with brisk flexion of the elbow and wrist, similar to those observed in patients after induction of anaesthesia. A second injection of rocuronium did not produce such pain and no movements were observed. We conclude that injection of rocuronium is associated with severe, burning pain of short duration, responsible for the spontaneous movements in the arm observed after induction of anaesthesia. (*Br. J. Anaesth.* 1997; **79**: 382–383).

Key words
Neuromuscular block, rocuronium. Pain, injection.

Rocuronium bromide is a new steroidal non-depolarizing neuromuscular blocking drug, related structurally to vecuronium and characterized by a rapid onset and intermediate duration of action.[1 2]

In the recent past, we observed in some patients the occurrence of sudden flexion, lasting 10–20 s, of the wrist and arm into which rocuronium was infused. Although this compound is considered to be tolerated well during injection, recent reports indicate severe burning pain after i.v. injection of rocuronium.[3–5]

The aim of this study was to assess and characterize the nature of the pain and to investigate the possible association between pain and spontaneous movements during administration of rocuronium.

Methods and results

After obtaining institutional Ethics Committee approval and informed patient consent, we studied 10 patients, ASA I, aged 20–40 yr, weighing more than 70 kg and undergoing elective orthopaedic surgery.

All patients were premedicated with midazolam 0.1 mg kg^{-1} orally, 1 h before induction of anaesthesia. An 18-gauge i.v. cannula was inserted into the dorsum of the hand and a tourniquet inflated slowly on the same side until the patient considered it uncomfortable; then it was deflated by 10 mm Hg in order to create venous stasis without any pain. In the first part of the study each patient received randomly, in a double-blind manner, both rocuronium 1 ml (10 mg) and 0.9% NaCl 1 ml (placebo) with an interval of 30-s in between. The vials were stored at room temperature at least 2 h before administration and were prepared and coded by an independent investigator. Thirty seconds after administration of the second drug, the tourniquet was deflated slowly and the patient received a bolus dose of propofol 3 mg kg^{-1} in order to assure rapid induction.

In the second part of the study another five patients received two successive injections of rocuronium 1 ml (10 mg) at 30-s interval, following the same procedure as described previously.

In the third part of the study 10 more patients received two successive injections of either 0.9% NaCl 1 ml (pH 5.3) or 0.9% NaCl 1 ml adjusted to a pH of 4, according to the same procedure as described previously. NaCl 0.9% was buffered at pH 4 by adding 20% hydrochloric acid 0.02 ml to 0.9% NaCl 1000 ml (ABL 505 Radiometer Copenhagen). The vials were prepared and coded by our pharmacist.

Pain was scored on a VAS from 0=no pain to 10=strongest pain imaginable. The patient, when pain was present, was asked to orally score its intensity and describe its nature. Any movement associated with pain was observed carefully by one of the investigators.

In the first part of the study no patient felt any pain (VAS=0) when receiving placebo. Eight of 10 patients complained of severe pain during injection of rocuronium (VAS=10) which lasted for approximately 10–20 s; one patient reported moderate pain (VAS=5) and the last patient an unpleasant feeling (VAS=2). The pain was described by all patients as

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A. BORGEAT, MD, D. KWIATKOWSKI, MD, Department of Orthopaedics, University of Zurich/Balgrist, Switzerland.
Accepted for publication: April 10, 1997.
Address for correspondence: Department of Orthopaedics, University of Zurich/Balgrist, Forchstrasse 340, CH-8008 Zurich, Switzerland.

intense and burning. The first eight patients had sudden flexion of the elbow and wrist at the same time; the two others showed only slight flexion of the wrist.

In the second part of the study all five patients complained of severe burning pain after the first injection with flexion of the elbow and wrist, as described previously (VAS=10). In contrast, after the second injection three patients had moderate pain (VAS=4) and the other two only an unpleasant feeling (VAS=2). All five patients reported that pain was greatly decreased during the second injection. No erythema or any change in the skin surrounding the point of injection or the arm was observed. Twenty-four hours later there was no vein induration and no patient complained of residual pain. At the end of the surgical procedure, patients recalled the pain, but none had any memory of respiratory difficulties.

In the third part of the study no patient complained of pain (VAS=0) when receiving either 0.9% NaCl pH 5.3 or 0.9% NaCl adjusted at pH 4.

Comment

We have demonstrated that administration of rocuronium was associated with severe burning pain on injection which lasted for approximately 10–20 s. In most cases brisk flexion of the elbow and wrist was observed simultaneously during i.v. injection of rocuronium. Interestingly, after a short interval of time, the pain was greatly decreased during a subsequent second administration of the drug.

Our results confirm earlier reports[3–5] describing the burning pain associated with administration of rocuronium before induction of anaesthesia. Of interest is the observation that the brisk flexion of the elbow and wrist noted in patients after induction of anaesthesia was similar in nature and duration to that observed in awake patients.

The mechanism by which rocuronium causes pain is unclear. Rocuronium is supplied in a sterile, nonpyrogenic, isotonic solution. Isotonicity is obtained with sodium chloride and a pH of 4 by adding acetic acid or sodium hydroxide. The osmolality (osmol litre^{-1}) and osmolarity (osmol kg^{-1}) are between 260 and 330.[6] The relatively low pH of the rocuronium solution may be a possible cause, as Klement and Arndt[7] have shown that injection of acidic solutions with a pH of 4 or less causes pain on injection, which increased linearly with a lower pH. However, the authors noted that after injection of acidic solutions, perivenous oedema developed immediately and was followed by thrombophlebitis for up to 3 weeks, which was not the case in this study.[7] Moreover, the absence of pain in patients receiving 0.9% NaCl 1 ml adjusted to pH 4 argues against such a possibility. Interestingly, vecuronium is buffered at a pH of 4 and has not been associated with pain on injection.

The short duration of the pain and marked decrease or absence of pain during a subsequent second administration led us to speculate that local release of mediators may be implicated in this reaction. Histamine is unlikely as neither erythema nor warmth in the surrounding tissue was observed or reported. Other mediators such as a kininogen cascade may be involved; this was postulated to explain the pain associated with propofol injection.[8] The pain associated with propofol and rocuronium is similar: it appears immediately during administration, duration is short and intensity decreases with subsequent injection.

Rocuronium should not be given to awake patients (e.g. priming). We believe that the similarities of movements of the arm observed in the awake patient and after induction of anaesthesia indicate that the movements observed in anaesthetized patients are the direct consequence of pain associated with administration of rocuronium. In order to avoid this side effect, it is important to inject rocuronium only when a deep stage of unconsciousness has been reached.

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Rapid tracheal intubation with propofol, alfentanil and a standard dose of vecuronium

R. GROENER AND D. G. MOYES

Summary

We studied 60 ASA I patients with Mallampati grade 1 airways to compare emergency intubating conditions with either alfentanil 20 μg kg^{-1}, propofol 2.5 mg kg^{-1} and vecuronium 0.1 mg kg^{-1}, or with thiopentone 5 mg kg^{-1} and suxamethonium 1 mg kg^{-1}. Ease of laryngoscopy, vocal cord status and cough response were graded. The trachea of all patients was intubated; 83% of patients in the alfentanil–propofol–vecuronium group and 86% in the thiopentone–suxamethonium group were considered to have satisfactory intubating conditions at 60 s. We conclude that the combination of alfentanil 20 μg kg^{-1}, propofol 2.5 mg kg^{-1} and vecuronium 0.1 mg kg^{-1} provided adequate conditions for rapid tracheal intubation. (*Br. J. Anaesth.* 1997; **79**: 384–385).

Key words
Anaesthetics i.v., propofol. Analgesics opioid, alfentanil. Neuromuscular block, vecuronium. Intubation tracheal, technique.

Techniques using non-depolarizing neuromuscular blocking agents in place of suxamethonium for rapid tracheal intubation have entailed the use of higher doses or priming techniques. Propofol and alfentanil given in combination facilitate intubation[1]; the addition of vecuronium 0.1 mg kg^{-1} has not been evaluated in the attempt to achieve intubation within 60 s. The aim of this study was to investigate if the combination of alfentanil, propofol and vecuronium would provide intubating conditions for rapid tracheal intubation comparable with those produced with thiopentone and suxamethonium.

Methods and results

After obtaining Ethics Committee approval, we studied 60 ASA I patients, aged 22–58 yr, with Mallampati class 1 airway anatomy,[2] fasted before operation and undergoing elective surgery. Patients were allocated randomly to one of two groups. All patients received glycopyrronium 5 μg kg^{-1} and their lungs were preoxygenated for 3 min. Patients in group A (n=30) received a bolus dose of alfentanil 20 μg kg^{-1}, followed 60 s later by propofol 2.5 mg kg^{-1} over 15 s and vecuronium 0.1 mg kg^{-1}. Patients in group B (n=30) received thiopentone 5 mg kg^{-1} over 15 s followed by suxamethonium 1 mg kg^{-1}.

Cricoid pressure was applied by an assistant. Laryngoscopy and intubation were performed using a Macintosh 3 blade, 60 s after administration of the neuromuscular blocking agent, by one of two experienced anaesthetists who entered the room 40 s after the blocker had been given and were blinded as to group allocation. After assessing intubating conditions this anaesthetist left the operating theatre and took no further part in the procedure.

Intubating conditions were assessed by the scoring system of Helbo-Hansen, Ravlo and Trap-Andersen.[3] Intubating conditions were judged acceptable when each individual category score was 2 or less. Ease of laryngoscopy, vocal cord status and degree of coughing are shown in table 1.

Table 1 Intubating conditions. One patient in group B was not scored for vocal cords or coughing (see text)

	Group A	Group B
Laryngoscopy		
Easy	23	23
Fair	6	4
Difficult	1	3
Impossible	0	0
Vocal cords		
Open	29	27
Moving	0	2
Closing	1	0
Closed	0	0
Cough response		
None	24	27
Slight	3	1
Moderate	3	1
Severe	0	0

Monitoring included electrocardiogram (ECG), pulse oximetry (Sp_{O_2}) and a calibrated non-invasive arterial pressure (NIAP) device (Dinamap, Critikon). Anaesthesia was continued using 1% halothane and 50% nitrous oxide in oxygen. Heart rate (HR), Sp_{O_2} and mean arterial pressure (MAP)

R. GROENER*, FCA (SA), D. G. MOYES, FRCA, Department of Anaesthesia, JG Strijdom and Baragwanath Hospitals, University of the Witwatersrand, Johannesburg, South Africa. Accepted for publication: March 27, 1997.

*Present address for correspondence: Department of Pediatric Anesthesiology, St Louis Children's Hospital, One Children's Place, St Louis, MO 63110, USA.

were obtained at 1-min intervals until 5 min after intubation.

Parametric data were analysed using the unpaired Student's *t* test and one-way ANOVA via the Instat program (Graphpad Software Inc, San Diego, CA, USA). Intubating condition scores were analysed using the chi-square test with Yates' correction, or with the Fisher exact probability test if the minimum chi-square conditions were not met.

The groups were comparable in age, sex and weight. Intubation was achieved in all patients. There were no significant differences in intubating condition scores between the two groups. Twenty-five of 30 patients (83%) in group A and 25 of 29 patients (86%) in group B had satisfactory intubating conditions. One patient in group B, despite a Mallampati 1 grading, had a Cormack and Lehane grade 3 view[4] at laryngoscopy and his trachea was not intubated at 60 s. This patient was the only one whose trachea was intubated with a bougie, at the first attempt, and was not scored for vocal cord status or cough response.

There was no decrease in oxygen saturation to less than 98% in either group. There was a significantly increased heart rate and MAP ($P<0.0005$) at each time in group B compared with group A.

Comment

When used as the sole agent for intubation, propofol is associated with an increased incidence of bucking and coughing. The addition of alfentanil 20 $\mu g\ kg^{-1}$ reduces but does not eliminate this problem.[1] Keaveny and Knell[5] reported a 95% success rate of intubation using propofol 2.5 mg kg^{-1} alone in 20 patients. However, Coghlan, McDonald and Csepregi[1] achieved successful intubation in only 73% of patients given propofol 2.5 mg kg^{-1} alone and in 83% using alfentanil 20 $\mu g\ kg^{-1}$ in addition to propofol. These success rates are unacceptable for rapid sequence intubation.

The onset time of vecuronium is dose-dependent. In this study a dose of $2 \times ED_{50}$ was used, which has an onset time of 2–3 min.[6] However, the combined use of propofol and alfentanil provided adequate conditions for rapid tracheal intubation within 60 s.

Higher doses of non-depolarizing neuromuscular blocking agents, or the use of priming techniques, are advocated when rapid sequence induction is indicated and the use of suxamethonium is undesirable. The disadvantages of prolonged neuromuscular block with higher doses of non-depolarizing agents, and the discomfort and risks associated with priming techniques, are avoided with the alfentanil–propofol–vecuronium technique. In the event of a failed intubation, however, the use of a non-depolarizing neuromuscular blocking agent in place of suxamethonium removes the option of early resumption of spontaneous ventilation.

We conclude that the combination of alfentanil 20 $\mu g\ kg^{-1}$, propofol 2.5 mg kg^{-1} and vecuronium 0.1 mg kg^{-1} provided adequate intubating conditions for rapid tracheal intubation and may be used when the use of suxamethonium is undesirable.

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Haemolysis after etomidate: comparison of propylene glycol and lipid formulations

A. DOENICKE, M. F. ROIZEN, R. HOERNECKE, M. MAYER, P. OSTWALD AND J. FOSS

Summary

We sought to determine if the solvent in the formulation of etomidate is responsible for haemolysis in patients. In a randomized, prospective, double-blind study of 49 patients undergoing otolaryngological surgery, patients received etomidate dissolved in propylene glycol or in lipid emulsion. Concentrations of free haemoglobin and haptoglobin were measured before and for up to 360 min after injection of etomidate. Free haemoglobin concentrations increased by 216.8 mg litre^{-1} in patients who received the propylene glycol formulation and by 11.8 mg litre^{-1} in the lipid emulsion group ($P \leq 0.0004$). Correspondingly, reductions in haptoglobin concentrations were significantly greater in the propylene glycol group ($P \leq 0.002$). We conclude that with respect to haemolysis, lipid emulsion is superior to propylene glycol as a solvent for etomidate. (*Br. J. Anaesth.* 1997; **79**: 386–388).

Key words

Formulations, etomidate. Anaesthetics i.v., etomidate. Complications, haemolysis. Blood, haemolysis.

We first suspected that etomidate formulated in propylene glycol causes haemolysis after observing a reddish discolouration of the sera of volunteers treated with etomidate dissolved in propylene glycol.[1] We suspected that this reflected intravascular haemolysis caused by the high osmolality of etomidate (4965 mosmol litre^{-1}) dissolved in propylene glycol.[2]

In this study we attempted to confirm the hypothesis that etomidate dissolved in propylene glycol causes haemolysis and that this is not associated with a more physiological solvent (lipid emulsion). In lipid emulsion, etomidate has a near physiological osmolality of 400 mosmol litre^{-1}.

Methods and results

After obtaining Institutional Review Board approval and informed consent, we studied 49 patients undergoing otolaryngological surgery, randomly allocated to receive etomidate in propylene glycol or in a lipid emulsion preparation for induction of anaesthesia. On the evening before and 1 h before operation, each patient was premedicated with lormetazepam 2 mg orally. Patients were given fentanyl 2 μg kg^{-1} i.v. and atracurium 0.07 mg kg^{-1} i.v. for induction of anaesthesia, followed 3 min later by etomidate 0.3 mg kg^{-1} i.v. Patients in the propylene glycol group received Hypnomidate (Janssen, Neuss, Germany), etomidate 2 mg ml^{-1} of an aqueous solution of 35 vol% propylene glycol. Patients in the lipid emulsion group received Etomidate-Lipuro (B. Braun, Melsungen, Germany), etomidate 2 mg ml^{-1} of fat emulsion consisting of soy bean oil, medium-chain triglycerides, egg lecithin and glycerol. Neuromuscular block was produced with atracurium 0.5 mg kg^{-1} i.v. before tracheal intubation. During induction with etomidate, patients' lungs were ventilated with oxygen; subsequently, they were ventilated using a mask and 1–1.5% isoflurane in oxygen without nitrous oxide. After tracheal intubation, anaesthesia was maintained with 0.5–1.2% isoflurane and 65% nitrous oxide in oxygen. During operation, fentanyl i.v. was administered as needed. At the end of surgery, all patients were given droperidol 1.25–2.5 mg i.v. A second dose of etomidate was not given during anaesthesia. Patients also received an infusion of 1500 ml of a balanced electrolyte solution to reduce the dilution effect of blood sampling.

To record and quantify haemolysis, free haemoglobin concentrations in plasma before and 5 min after administration of etomidate were measured by an antigen–antibody nephelometer test. As an additional measure of haemolysis, haptoglobin concentrations in serum were measured by enzyme immunoassay before and 120, 240 and 360 min after administration of etomidate. At each measurement time, packed cell volume (PCV) was

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ALFRED DOENICKE*, MD, RAINER HOERNECKE, MD, MICHAEL MAYER, MD, PHILIPP OSTWALD, MD, Institute for Anaesthesiology, Ludwig-Maximilians University, Munich. MICHAEL F. ROIZEN, MD (Department of Anesthesia and Critical Care); JOSEPH FOSS, MD (Department of Anesthesia and Critical Care and the Committee on Clinical Pharmacology); University of Chicago, Chicago, IL, USA. Accepted for publication: April 8, 1997.

*Address for correspondence: Institute for Anaesthesiology, Ludwig-Maximilians University of Munich, Pettenkoferstr. 8a, 80336 Munich, Germany.

Table 1 Comparison of serum free haemoglobin (mg litre^{-1}) and serum haptoglobin (g litre^{-1}) concentrations in the two groups. Serum haptoglobin concentrations are corrected for changes in packed cell volume. Values are (mean (SEM))

Time of measurement	Etomidate in propylene glycol ($n=24$)	*P* value compared with baseline	Etomidate in lipid emulsion ($n=25$)	*P* value compared with baseline	*P* value between groups
Free haemoglobin					
Baseline	42.2 (9.3)		42.3 (9.3)		0.996
5 min	259.0 (15.1)	0.0004	54.1 (5.7)	0.289	0.0004
Haptoglobin					
Baseline	1.78 (0.15)		1.79 (0 13)		0 950
120 min	1.10 (0.13)	0.0004	1.47 (0.13)	0.0004	0 042
240 min	0.85 (0 11)	0.0004	1.36 (0.12)	0.0004	0.003
360 min	0.84 (0.11)	0.0004	1.39 (0.13)	0.0004	0.002

also measured, and correction in haptoglobin concentrations was made for the dilution effect. The *t* test for non-paired samples and covariance analysis was used for statistical analysis with $P \leq 0.05$ considered statistically significant.

The two groups did not differ in age, height, weight, sex distribution, duration of procedure or dose of etomidate received. PCV values did not differ between groups. Mean free haemoglobin concentrations after etomidate in propylene glycol increased significantly from 42.2 (SEM 9.3) mg litre^{-1} at baseline to 259 (15.1) mg litre^{-1} 5 min later ($P \leq 0.0004$) and in the lipid emulsion group from 42.3 (9.3) to 54.1 (5.7) mg litre^{-1} ($P=0.289$) (table 1). Between-group differences were significant 5 min after administration of etomidate ($P \leq 0.0004$).

Serum haptoglobin concentrations decreased significantly compared with baseline in both groups after administration of etomidate. The reduction in free haptoglobin after etomidate in propylene glycol was significantly greater after 240 and 360 min ($P \leq 0.003$ and $P \leq 0.002$, respectively) (table 1).

Comment

Several adverse effects caused by propylene glycol have been described: hypotension, pain on injection, lactic acidosis and pulmonary hypertension.[1 3–5] In our study, a single injection of etomidate 0.3 mg kg^{-1} dissolved in propylene glycol increased free haemoglobin (514%) and decreased serum haptoglobin (52.8%) concentrations significantly, indicating intravascular haemolysis. Free haemoglobin is bound within a few minutes by haptoglobin, forming a haptoglobin–haemoglobin complex. The half-life of haptoglobin is 3–4 days compared with that of the haptoglobin–haemoglobin complex of only 8 min. If intravascular free haemoglobin increases, haptoglobin concentration decreases, which is a measurable sign of haemolysis.

Haemolysis and cell lysis associated with an induction dose of etomidate dissolved in propylene glycol may not cause detectable renal injury in healthy individuals. However, several other drugs are also dissolved in propylene glycol such as lorazepam (osmolality 12800 mosmol litre^{-1}) and nitroglycerin (osmolality 4550 mosmol litre^{-1}).[2] Combined use of drugs dissolved in propylene glycol may increase the likelihood and severity of haemolysis. If etomidate dissolved in propylene glycol or other drugs with similar formulations are injected repeatedly after short intervals, or if they are used in combination, circulating haptoglobin may be depleted completely. Under such circumstances free haemoglobin from haemolysis may exceed binding capacity and exert toxic effects.[6]

Intraoperative autotransfusion in patients who have received etomidate dissolved in propylene glycol also makes haemolysis problematic. It has been shown that infusion of packed red cells, especially from autotransfusion, decreases haptoglobin concentrations.[7] In fact, haptoglobin was undetectable in seven of 47 patients after autotransfusion. Etomidate is a desirable induction agent for older, less healthy patients because it does not effect cardiovascular stability. These patients often undergo procedures (total hip replacement or vascular surgery) that use autotransfusion. In such patients, the combined effects of etomidate in propylene glycol and autotransfusion may decrease haptoglobin concentrations. We speculate that those likely to be affected include patients with other risk factors, such as impaired renal function or patients in shock who need high re-transfusion volumes.

Our results are consistent with the hypothesis that propylene glycol is a less safe vehicle than lipid emulsion for etomidate. Side effects associated with propylene glycol may be toxic for some patients.

Acknowledgements

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Enhanced choline acetyltransferase activity does not explain the action of inhaled convulsants

R. GRIFFITHS, P. IONESCU, Z. FANG, D. D. KOBLIN AND E. I. EGER

Summary

Enhancement of choline acetyltransferase (ChAT) activity and increased intraneuronal acetylcholine (ACh) may explain the convulsant activity of some inhaled compounds. Enflurane, for example, enhances such activity. Accordingly, we measured choline acetyltransferase (ChAT) activity in rat cortical synaptosomes in the presence of two inhaled convulsants, flurothyl ($CF_3CH_2OCH_2CF_3$) and 1,2-dichlorohexafluorocyclobutane at partial pressures below and greatly exceeding those which produce convulsions *in vivo*. Neither agent changed the kinetic parameters, maximum velocity (*v*max) or Michaelis constant (K_m). The *v*max for controls in the flurothyl series was 016 (0.06) nmol mg^{-1} min^{-1} and the K_m was 0.23 (0.11) mmol $litre^{-1}$. For the 1,2-dichlorohexafluorocyclobutane series of experiments the results for the controls were *v*max 0.23 (0.10) nmol mg^{-1} min^{-1} and K_m 0.20 (0.08) mmol $litre^{-1}$. Modification of ChAT activity did not contribute to the excitatory effects of these agents. (*Br. J. Anaesth.* 1997; **79**: 389-391).

Key words
Anaesthetics volatile. Enzymes, choline acetyltransferase. Nerve, neurotransmitters. Complications, convulsions.

Acetylcholine (ACh) is an excitatory neurotransmitter important for arousal and maintenance of consciousness.[1] The central cholinergic system may also play a role in the genesis of seizure.[2]

Enflurane enhances the activity of the enzyme responsible for ACh synthesis, choline acetyltransferase (ChAT).[3] To determine if this effect applies broadly, we investigated the effects of two volatile compounds with known convulsant properties, flurothyl and 1,2-dichorohexafluorocyclobutane, on the kinetics of ChAT in rat cortical synaptosomes.

Methods and results

With approval from the University of California San Francisco Committee on Animal Research, we studied 52 male (300–430 g), specific pathogen-free Sprague Dawley rats from Charles River Laboratories. Four rats were placed in individual plastic cylinders and the tail end of each cylinder had a rubber stopper with multiple holes. The tail and a rectal temperature probe passed through two of these holes, and the tail was secured with tape to a plastic extension of each cylinder.

Each cylinder was inserted into a slightly larger individual plastic chamber. A catheter for sampling inspired gas in the chamber and another tube for delivery of gases traversed the stopper at the "head" end of the chamber. Oxygen was flushed through the tube before beginning the study. The tubes at the tail ends were connected to a carbon dioxide adsorbent canister containing 200 g of fresh soda lime. To complete the system, the adsorbent canister was connected to a circulating fan that led to the head-end tubes. To permit delivery of compounds, we added a "T" connector between the carbon dioxide adsorber and the tail end of the four chambers. Finally, the system was connected with a demand oxygen supply (bypass flow approximately 50 ml min^{-1}) for delivery of oxygen after closure of the system.

We initially flushed the system until the oxygen concentration was 95% or higher. Oxygen concentration was measured with a Pauling (polarographic) meter (Beckman model E2). After closing the system (oxygen supplied on demand), flurothyl (>99% purity, PCR Inc., Gainesville, FL, USA) or 1,2-dichlorohexafluorocyclobutane (>97% purity, PCR Inc., Gainesville, FL, USA) was introduced in sequentially increasing concentrations as liquid aliquots followed by a flush of oxygen. For each concentration, a 20-min equilibration period was allowed, during which we observed the rats for convulsion. If no convulsion occurred, we increased the concentration by 15–25%. The ED_{50} for convulsion was defined as the mean of the partial pressures in the chamber immediately below and just causing a convulsion.

RICHARD GRIFFITHS*, MD, FRCA, University Department of Anaesthesia, Leicester Royal Infirmary, Leicester LE1 5WW. POMPILIU IONESCU, MD, ZEXU FANG, MD, EDMOND I. EGER II, MD, Department of Anesthesia, University of California, San Francisco, CA, USA. DONALD D. KOBLIN, PHD, MD, Anesthesiology Service, Department of Veterans Affairs Medical Center, San Francisco, CA, USA Accepted for publication: April 25, 1997.

*Present address for correspondence: Department of Anaesthesia, Peterborough District Hospital, Peterborough PE3 6DA.

Table 1 Effect of flurothyl and 1,2-dichlorohexafluorocyclobutane on choline acetyltransferase (ChAT) kinetic parameters, maximal velocity (*v*max) and Michaelis constant (K_m) (mean (SD)). Actual flurothyl concentrations measured at the end of the experiments were, mean 0.11 (SD 0.0035), 0.21 (0.0064), 0.43 (0.017), n=20. Actual 1,2-dichlorohexafluorocyclobutane concentrations measured at the end of the experiments were 2.11 (0.15), 4.13 (0.28), 8.86 (0.52), n=20

	Flurothyl (target concentrations)			
Kinetic parameter	Air	0.125 %atm	0.25 %atm	0.5 %atm
*v*max (nmol mg^{-1} min^{-1})	0.16 (0.06)	0.16 (0.06)	0.14 (0.01)	0.14 (0.03)
K_m (mmol litre^{-1})	0.23 (0.11)	0.22 (0.09)	0.21 (0.08)	0.21 (0.10)
	1,2-dichlorohexafluorocyclobutane (target concentrations)			
Air	2.5 %atm	5.0 %atm	10 %atm	
*v*max (nmol mg^{-1} min^{-1})	0.23 (0.10)	0.25 (0.10)	0.25 (0.10)	0.20 (0.06)
K_m (mmol litre^{-1})	0.20 (0.08)	0.19 (0.04)	0.20 (0.05)	0.17 (0.03)

The convulsive ED_{50} values for flurothyl and 1,2-dichlorohexafluorocyclobutane, respectively, were mean 0.156 (SD 0.004) %atm, n=24 and 5.54 (0.01) %atm, n=28.

With approval from the UCSF Committee on Animal Research, we prepared synaptosomes from the cortex of male Fisher rats (200–250 g) using the method described by Dunkley and colleagues.[4]

ChAT activity was determined using the method of Fonnum.[5] Synaptosomes were suspended (0.5 ml) in a medium containing NaCl 300 mmol litre^{-1}, ethylenediaminetetra-acetic acid (EDTA) 20 mmol litre^{-1}, neostigmine 1 mmol litre^{-1}, 0.5% (w/v) Triton X-100 and sodium phosphate 50 mmol litre^{-1} (pH 7.4), to a protein concentration of 0.5 mg ml^{-1}. The mixture was placed in a 10-ml gas-tight syringe containing either air or air and one of the test gases, and incubated in a water bath at 37°C for 10 min. Constant shaking allowed equilibration of the test gas with the synaptosome suspension. A substrate mixture (0.5 ml) containing choline bromide at concentrations of 0.05–2.00 mmol litre^{-1}, acetyl coenzyme A 2 mmol litre^{-1} and [^{3}H]acetyl coenzyme A 0.5° μCi in the incubation medium but without Triton X-100 was added to the synaptosome suspension, shaken gently and returned to the water bath for 30 min. Immediately after addition of the substrate mixture a 100-μl aliquot was withdrawn and ACh extracted using Kalignost (Koch-Light Lab Ltd, Bucks, UK).[5] These samples were used as time zero controls for background subtraction of radioactivity from the test samples. After 30 min, 100-μl samples were obtained in duplicate and ACh content measured by scintillation counting after Kalignost extraction.[5]

The concentration of test gas in the syringes at the end of the incubation was measured by gas chromatography. The synaptosome preparations were exposed to air with flurothyl at 0.125, 0.25 and 0.5%atm. The concentrations of 1,2-dichlorohexafluorocyclobutane in air were 2.5, 5.0 and 10.0%atm. Controls, exposed to air only, were included in each set of experiments.

Michaelis–Menten kinetic parameters, maximum reaction velocity (*v*max) and Michaelis constant (K_m) were calculated for ChAT in each experiment using rectangular hyperbola curve fit in SigmaPlot for Windows. Results were compared using Student's paired t test. $P<0.05$ was considered statistically significant.

Neither compound altered the kinetics of ChAT at any concentration tested (table 1).

Comment

Our previous work demonstrated that anaesthetizing concentrations of enflurane decreased the K_m of ChAT for choline bromide.[3] These findings led to our hypothesis that the convulsant effect of inhaled convulsants might result from enhancement of ChAT activity. The cholinergic system has been implicated in the genesis of seizures.[2] These findings are consistent with our hypothesis.

In conflict with our hypothesis, our results demonstrated that flurothyl and 1,2-dichlorohexafluorocyclobutane did not alter the kinetics of ChAT from rat cortical synaptosomes. There is a remote possibility that the lack of effect seen with the synaptosome preparation resulted from the different strain of rat used for the ChAT part of the experiment. Test concentrations of both agents were distributed either side of the convulsive ED_{50} for these agents *in vivo* in rats. It remains possible that ChAT kinetics were affected in amounts too small to be measured. However, in previous studies with enflurane,[3] a 35% decrease in the K_m of ChAT was detected, and a greater decrease would be expected in our experiments if ChAT kinetics were important.

Many other transmitter systems are also involved in the genesis of seizures and it may be that discrete mechanisms explain the epileptic capacity of each convulsant. At the crab neuromuscular junction, flurothyl selectively blocks inhibitory transmission (GABA) more than excitatory transmission (glutamate).[6]

Although the synaptosome preparation contains the machinery needed for neurotransmitter studies, the preparation has limitations which may influence the interpretation of this study. The preparation produces synaptosomes from nerve endings secreting diverse transmitters, not just ACh. Thus there is still the possibility of non-physiological crosstalk that could obscure drug effects. To summarize, the heterogeneous nature of the synaptosome preparation, together with the potential presence of more than one transmitter in cholinergic neurones, limits the interpretation of results from our system.

Although we found that modulation of ChAT activity does not contribute to the excitatory effects of volatile convulsants, this does not exclude ACh metabolism as a cause of the effects of such compounds and future studies may focus on other aspects of cholinergic function.

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British Journal of Anaesthesia 1997; **79**: 392–393

CASE REPORTS

Sevoflurane for difficult tracheal intubation

S. M. MOSTAFA AND A. M. J. ATHERTON

Summary

Three patients in whom difficult tracheal intubation was expected but awake fibreoptic intubation was not feasible presented for head and neck surgery. Anaesthesia was induced rapidly and smoothly by inhalation of sevoflurane followed by fibreoptic or conventional tracheal intubation. (*Br. J. Anaesth.* 1997; **79**: 392–393).

Key words

Anaesthetics volatile, sevoflurane. Intubation tracheal, difficult.

Sevoflurane is becoming regarded as the agent of choice for inhalation induction of anaesthesia. Several studies have demonstrated that rapid and smooth induction is possible with sevoflurane.[1–6] However, inhalation induction with this agent has not been reported in the management of a difficult airway. We report three patients in whom we chose to induce anaesthesia by inhalation of sevoflurane because difficulty in managing the airway was anticipated and other techniques were not suitable.

Case reports

Patient No. 1

A 68-yr-old man with a carcinoma of the left maxillary sinus presented for radical maxillectomy, cervical lymph node dissection and reconstructive surgery. He was hypertensive and had chronic lung disease. He had restricted mouth opening. Nasal intubation was not possible because both nostrils were occluded by the tumour. Awake fibreoptic intubation under local anaesthesia was likely to be impossible because of intraoral protrusion of the tumour, excessive secretions and blood in the oropharynx. The patient refused tracheotomy under local anaesthesia.

After premedication with temazepam 10 mg orally and glycopyrronium 200 μg, a 16-gauge i.v. cannula was inserted and a crystalloid infusion was commenced. Droperidol 2.5 mg and fentanyl 50 μg were given i.v. Standard monitoring included pulse oximetry and ECG. Oxygen was given for 5 min via a circle system with a close fitting mask followed by up to 4% sevoflurane and 66% nitrous oxide in oxygen. After 120 s anaesthesia was sufficiently deep to allow tracheal intubation with a cuffed 7.0-mm tube passed over a flexible fibreoptic laryngoscope (LF2, Keymed plc, UK). Thereafter, anaesthesia was maintained with isoflurane and nitrous oxide in oxygen, with increments of atracurium and fentanyl. Both surgery and anaesthesia were uneventful.

Patient No. 2

A 45-yr-old man presented for parathyroidectomy. Conventional intubation had been impossible during a previous anaesthetic. He was educationally subnormal, obese and had poor neck extension, coarse features with a large tongue, and very restricted mouth opening with only a few remaining teeth which were in poor condition. It was decided that conventional oral intubation would fail. He was unlikely to co-operate with awake intubation or tracheotomy. Therefore, it was decided to perform nasotracheal fibreoptic intubation.

He was premedicated with temazepam 10 mg orally and glycopyrronium 200 μg. He was given 100% oxygen for 5 min. Nitrous oxide 50% in oxygen was introduced with increasing concentrations of sevoflurane up to 7%. Initially maintaining a clear airway during anaesthesia proved to be difficult. Oxygen 100% was given until lightening of anaesthesia led to improvement in airway patency. Anaesthesia was administered successfully via the left nostril using a nasopharyngeal airway attached to a 15-mm tracheal tube connector and catheter mount connected to the anaesthetic system. Sevoflurane was reintroduced. A sufficient depth of anaesthesia was achieved and successful nasotracheal intubation was accomplished via the right nostril using a flexible fibreoptic laryngoscope. Anaesthesia for surgery was maintained as in the previous patient. The tracheal tube was removed at the end of surgery with the patient awake.

Patient No. 3

A 32-yr-old ASA III woman underwent uneventful resection of a left maxillary neuroblastoma with radical maxillectomy, orbital exenteration and resection of the nasal septum. She presented 5 days after this procedure for change of the obturator and packing.

S. M. MOSTAFA, FRCA, A. M. J. ATHERTON*, FRCA, Department of Anaesthesia, Royal Liverpool University Hospital, Prescot St, Liverpool L7 8XP. Accepted for publication: April 22, 1997.

*Present address: Department of Anaesthesia, Cardiothoracic Centre, Thomas Drive, Liverpool, L14 3PE.

Her inter-incisor distance was only 2 cm at full mouth opening because of masseter spasm. There was no nasal airway as the septum had been removed and the cavity packed. Local anaesthesia for the oropharynx and larynx was inappropriate and unlikely in view of the previous surgery.

As surgery did not involve the temporomandibular joint, mouth opening was likely to improve allowing easy maintenance of the airway after induction of anaesthesia. It was decided that inhalation induction would be appropriate, followed by conventional or fibreoptic laryngoscopy.

She was given midazolam 3 mg and glycopyrronium 200 μg i.v. on arrival in the anaesthetic room. Her lungs were preoxygenated for 5 min. Anaesthesia was induced with up to 4% sevoflurane in oxygen. Her jaw relaxed and it was possible to introduce a McCoy laryngoscope blade and to view the arytenoid cartilages with flexion of the laryngoscope tip. Therefore, suxamethonium 100 mg was given and the trachea was intubated with the aid of a gum elastic bougie. Thereafter anaesthesia and surgery were uneventful.

Discussion

Inhalation induction of anaesthesia is a well recognized technique in the management of the difficult airway. Its inherent safety depends on gradual and smooth deepening of anaesthesia. If loss of muscle tone leads to loss of airway patency then anaesthesia inevitably lightens with return of muscle tone. We believe that sevoflurane offers major advantages compared with the usual agent, halothane. Many of our patients have had recent anaesthesia for endoscopy or biopsy and repeated halothane anaesthesia should be avoided where possible. Induction is smoother, faster and more pleasant than with halothane or isoflurane,[1–6] with less coughing and breath-holding. If airway patency is lost, the lower blood solubility of sevoflurane leads to faster awakening. Although we used nitrous oxide in two of our patients, as we would have previously when using halothane, use of 100% oxygen as a carrier gas delays desaturation if obstruction occurs. Use of halothane without nitrous oxide sacrifices the benefit of the second gas effect resulting in a slower induction, whereas induction with sevoflurane in oxygen remains highly satisfactory, as in patient No. 3. Sevoflurane therefore offers a greater margin of safety than halothane in the management of the patient with a difficult airway.

Induction of anaesthesia in two of our three patients was smooth and fast. The third patient briefly developed airway obstruction but this was overcome readily without hypoxia. At no time during induction did Sp_{O_2} decrease to less than 96% in any of our patients. Oxygenation and ventilation, as confirmed by pulse oximetry and capnography, were satisfactory throughout induction in two of the three patients. The second patient briefly developed airway obstruction during induction. This was caused partially by loss of the airway before adequate depth of anaesthesia for intubation was achieved. This resulted mainly from the patient's abnormal anatomy. The obstruction was overcome by insertion of a nasopharyngeal airway before significant desaturation had occurred. Intubation was easy and rapid. The use of a laryngeal mask in these patients was not possible because of limited mouth opening and the type of surgery to be undertaken.

Concerns regarding sevoflurane cost and degradation by soda lime do not apply if it is used purely for induction. We have since used sevoflurane for inhalation induction in similar patients with success. We conclude that sevoflurane appears to be a useful agent for inhalation induction in patients with difficult airways and merits further investigation.

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Transient radicular irritation after spinal anaesthesia with 2% isobaric lignocaine

D. RAMASAMY AND R. EADIE

Summary

A typical case of transient radicular irritation after spinal anaesthesia with 2% isobaric lignocaine is described. The definition and history of this syndrome and the implications of the use of pencil point needles with lignocaine for spinal anaesthesia are discussed. (*Br. J. Anaesth.* 1997; **79**: 394–395).

Key words

Anaesthetic techniques, subarachnoid. Anaesthetics local, lignocaine. Complications, transient radicular irritation.

In the past 5 yr, 5% hyperbaric lignocaine has been implicated increasingly in the cause of neurotoxicity after spinal anaesthesia. Its association with the cauda equina syndrome in continuous spinal anaesthesia with microcatheter techniques has been documented previously.[1] Sacral accumulation of the local anaesthetic (caused partly by the low flow rates of the hyperbaric solution through the microcatheter) together with its neurotoxicity were thought to be responsible.

It became apparent that the use of 5% lignocaine with pencil point spinal needles may also cause transient neurological deficits.[2 3] The term "transient radicular irritation" (TRI) has been used to describe such deficits. Pinczower and colleagues[4] noted some features common to this syndrome involving the use of 5% hyperbaric lignocaine. These were mainly: (1) bilateral radicular-like leg pain with or without back pain; (2) moderate or severe pain; (3) onset of pain within 24 h of surgery; (4) duration of pain greater than 24 h; and (5) no previous history of severe back or leg pain.

More recently 2% hyperbaric,[5] and now 2% isobaric solutions of lignocaine have also been implicated in TRI.[6 7]

We report a case of TRI which occurred when 2% plain isobaric lignocaine was injected through a 27-gauge Whitacre needle, when the aperture of the needle was directed caudally.

Case report

A 62-yr-old man presented for cystoscopy having been admitted in urinary retention. He had undergone cystoscopy, bladder neck incision and a transurethral resection of his prostate (TURP) 1 month previously, having had a 12-month history of hesitancy and frequency. This had been performed under an uneventful spinal anaesthetic using 0.5% heavy bupivacaine 2 ml via a 27-gauge Whitacre needle.

His past history included coronary artery bypass grafts in 1982, hypertension and congestive heart failure. He still had symptoms of angina with moderate exercise. He had no history of diabetes or chronic back pain. His medications included nifedipine, enalapril, frusemide, amiloride and aspirin. Routine preoperative tests, including a clotting profile, were within normal limits.

On this occasion, atraumatic dural puncture was performed in the sitting position at the first attempt at the L3–4 interspace, using a 27-gauge Whitacre needle. The side port of the spinal needle was directed caudally and injection of 2% plain isobaric lignocaine 3 ml was given over 4–5 s. No discomfort was elicited during insertion of the spinal needle or during injection of the local anaesthetic.

Cystoscopy, carried out in the lithotomy position, was uneventful and of short duration. Necrotic tags in the previous resection cavity were excised and adhesions to the verumontanum were divided. The patient remained haemodynamically stable during the procedure.

Twelve hours after operation, in the ward, he developed bilateral "burning" pain radiating from his buttocks to mid calves. This was uncomfortable enough for him to request oral analgesia (paracetamol–codeine) from which he gained partial relief. In particular he gave no history of motor symptoms and was able to walk freely. He had no headache, tinnitus or diplopia.

On examination he was afebrile and had no evidence of sensory loss or motor weakness, although he had diminished ankle jerks in comparison with his knee jerks. There was no record of his lower limb reflexes on admission. Sphincter tone was normal.

It was decided after consultation to treat him conservatively and his symptoms settled over the next 5 days. His urinary catheter was removed 2 days after operation and he voided successfully. He was

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D. RAMASAMY*, MB, BS, MRCP, DCH, DA, R. EADIE, MB, BS, FANZCA, Department of Anaesthesia, Launceston General Hospital, Launceston, Tasmania. Accepted for publication: April 30, 1997.

*Address for correspondence: Department of Anaesthesia, Royal Hobart Hospital, Liverpool Street, Hobart, Tasmania, Australia 7000.

discharged 5 days after operation. He was reviewed 4 months later with no recurrence of sensory symptoms. In particular, his ankle jerks, although present, were still diminished.

Discussion

The potential neurotoxicity of 5% hyperbaric lignocaine has been investigated *in vitro* by Lambert, Lambert and Strichartz[8] using desheathed bullfrog sciatic nerves. These nerves bear some resemblance to the similarly unprotected cauda equine in mammals. They found that exposing the nerve fibres to 5% lignocaine with or without 7.5% glucose for 15 min produced irreversible conduction block. Indeed there was no recovery of the compound action potential (CAP) in nerve fibres exposed to 5% lignocaine in 7.5% glucose for 3 min or longer. Furthermore, exposure to 1.5% lignocaine for 15 min produced partially reversible conduction block.

Bainton and Strichartz[9] studied the effect of 15 min exposure of (≈1%) lignocaine 40 mmol litre^{-1} on the CAP of frog sciatic nerves. After a washout period of 2 h with Ringer's solution, the CAP remained degraded. This could not be explained simply on the basis of concentrations of residual lignocaine present after washout. It appears therefore that some local anaesthetics, if present in sufficiently high concentrations, may be potentially neurotoxic. Beardsley and colleagues[10] investigated maldistribution of hyperbaric solutions of dye in spinal models using Whitacre and Quincke spinal needles. They suggested that the type and gauge of the spinal needle, speed of injection and direction of the needle may contribute to maldistribution of the local anaesthetic in the spinal canal. Interestingly they suggested that exposure to peak concentrations of more than 2% lignocaine may be the clinical threshold for toxicity. They had deduced this from peak sacral dye concentrations found after injections which were directed sacrally through 25- and 27-gauge Whitacre needles.

In clinical practice, Tarkkila, Huhtala and Tuominen[11] studied 600 patients who underwent spinal anaesthesia. They found that 10% of patients anaesthetized with 5% lignocaine had transient neurological symptoms similar to those described by our patient. They concluded that the use of 5% hyperbaric lignocaine for spinal anaesthesia should be reconsidered. Hampl and colleagues[12] studied 276 patients undergoing elective gynaecological and obstetric surgery under spinal anaesthesia with either 5% hyperbaric lignocaine or hyperbaric bupivacaine. They found a 37% incidence of pain and dysaesthesia in those who received hyperbaric lignocaine. This was typically bilateral, involved the thighs and back, and persisted for less than 3 days.

We suggest that our patient's symptoms may have been caused by a neurotoxic concentration of lignocaine at the sacral nerve roots. Unlike the hyperbaric solution where a low flow rate contributes to maldistribution, the high speed of injection with the isobaric solution and the sacral direction of the Whitacre needle probably contributed to the caudal deposition of the local anaesthetic.

It is unlikely that trauma played a causative role as there was no discomfort elicited on placing the spinal needle and the symptoms were bilateral.

As the patient remained haemodynamically stable, ischaemia was also unlikely. Chronic lumbar disc pathology was also probably unlikely as he had no history of chronic back pain. Furthermore, 2% lignocaine has been reported previously to cause a cauda equine syndrome,[13] although this involved accidental intrathecal injection of 2% lignocaine 32 ml intended for extradural anaesthesia.

Pinczower and colleagues,[4] in a study of 17 cases, implicated 2% isobaric lignocaine in the cause of neurotoxicity, although no patient had symptoms typical of their definition of TRI. More recently, Hampl and colleagues[5] found that the incidence of TRI was similar with 2% hyperbaric lignocaine and 5% hyperbaric solutions. Furthermore, Pollock and colleagues,[6 7] implicated 2% isobaric and 5% hyperbaric solutions of lignocaine in causing similar rates of TRI.

In summary, we believe that the use of 5% hyperbaric lignocaine and 2% isobaric lignocaine for spinal anaesthesia should be re-evaluated and that the possible maldistribution of local anaesthetics intrathecally and their consequences should be considered when directing pencil point needles caudally.

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Unsuspected difficult intubation caused by a laryngeal web

Z.-K. CHONG, B. JAWAN, Y.-Y. POON AND J.-H. LEE

Summary

We report a case of unsuspected difficult intubation in an adult caused by laryngeal web formation in the anterior commissure of the larynx. After induction of anaesthesia, most parts of the posterior commissure of the vocal cords were seen clearly at laryngoscopy, but a 7.5-mm internal diameter (id) tracheal tube could not be advanced below the level of the vocal cords because of resistance. Intubation was re-attempted several times after oxygenation by mask with trials of smaller tubes. Finally, a 5.0-mm id cuffed tube was passed successfully through the vocal cords, and secured in place. Because of the unexpected difficulties in intubation, an otolaryngologist was consulted to examine the larynx with a microscope. A web of 0.5 cm in the anterior commissures was found which caused subglottic stenosis. (*Br. J. Anaesth.* 1997; **79**: 396–397).

Key words
Larynx, dammage. Larynx, laryngoscopy. Complications, stenosis. Intubation tracheal, difficult.

We present a rare case of difficult intubation in an adult after induction of anaesthesia caused by a laryngeal web.

Case report

A 65-yr-old male, ASA II, was admitted for radical nephroureterectomy because of malignant obstructive uropathy. Past surgical history included laparotomy under general anaesthesia more than 30 yr previously and extracorporeal shock wave lithotomy (ESWL) twice under i.v. general anaesthesia without tracheal intubation in the past month. Medical history revealed that pulmonary tuberculosis had been diagnosed and treated decades ago. Mild hoarseness without dyspnoea was noted. Laboratory data, including electrocardiogram, haematology and serum electrolytes, were normal. Chest x-ray revealed minimal fibrotic pulmonary tuberculosis in the right upper lung. General anaesthesia was induced with fentanyl 100 μg and 2.5% thiopentone 300 mg i.v. No premedication was given.

Suxamethonium 60 mg was given to facilitate tracheal intubation. Most parts of the posterior commissure of the vocal cords were seen clearly at laryngoscopy, but a 7.5-mm internal diameter (id) tracheal tube could not be advanced below the level of the vocal cords because of resistance. Intubation was re-attempted several times after oxygenation by mask with trials of smaller tubes. Finally, a 5.0-mm id cuffed tube was passed successfully through the vocal cords and secured in place. Because of the unexpected difficulties during intubation, an otolaryngologist was consulted to examine the larynx with a microscope. A web of 0.5 cm in the anterior commissures was found (fig. 1) which caused subglottic stenosis. The arytenoids, vocal cords and epiglottis were free of disease or tumour. The consultant advised no treatment because the web caused only mild hoarseness without any other symptoms. Bronchial culture was obtained. The operation was carried out as scheduled and the patient's trachea was extubated uneventfully in the post-anaesthesia recovery room. There was no respiratory problem noted during hospitalization. The patient was discharged from hospital 1 week later.

Discussion

The cause of difficult intubation in our case was extremely rare. There are only a few reports of difficult intubation caused by laryngeal web in the literature.[1–3] All were not suspected before induction of anaesthesia and most resulted in morbidity. Emergency tracheostomy was necessary before operation to maintain airway patency in one adult,[1] and after operation in two children because of airway obstruction after extubation.[2, 3] Severe respiratory distress was also noted in a child. Laryngeal webs consist of thin transparent or thick fibrous membranes and may be congenital or acquired. Congenital webs, usually symptomatic in infancy or early childhood, are the result of incomplete recanalization of the primitive laryngeal airway.[4] Their incidence has been estimated at approximately 1 in 10 000 births. Seventy-five percent of laryngeal webs are located at the level of the vocal cords, the remainder being either sub- or supraglottic. The

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ZU-KONG CHONG*, MD, BRUNO JAWAN, MD, YAN-YUEN POON, MD, JU-HAO LEE, MD, Chang Gung Memorial Hospital, Kaohsiung Medical Center, Department of Anesthesiology, 123, Ta-Pei Road, Niao Sung Hsiang, Kaohsiung Hsien, Taiwan, ROC. Chang Gung Medical and Technical College, Taipei, Taiwan. Accepted for publication: April 21, 1997.

*Address for correspondence: Chang Gung Memorial Hospital, Kaohsiung Medical Center, Department of Anesthesiology, 123, Ta-Pei Road, Niao Sung Hsiang, Kaohsiung Hsien, Taiwan, ROC.

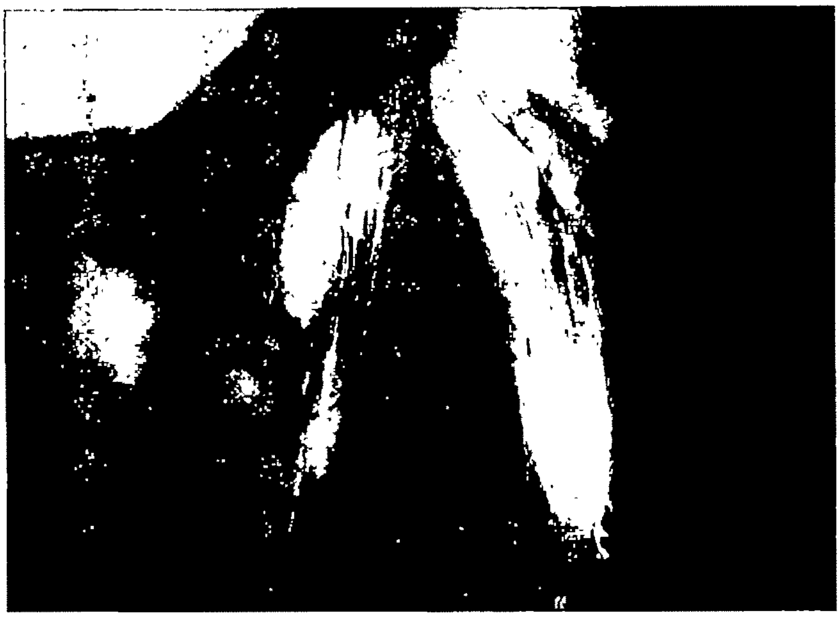

Figure 1 A laryngeal web of approximately 0.5 cm in the anterior commisure of the larynx, which caused subglottic stenosis, was seen clearly under a microscope

majority of glottic webs lie anteriorly between the cords; only 1–2% are located posteriorly.[5] The disease is suggested by clinical symptoms such as stridor, weak crying and feeding problems, but endoscopic vision is essential for a definite diagnosis.[6] Usually the symptomatic laryngeal web is treated by one of the following surgical procedures: surgical division, endoscopic insertion of a keel or laser treatment.[6 7] Webs without any clinical symptoms are not treated as the incised and divided adjacent cords may adhere together because of scarring.

The aetiology of laryngeal web formation in our patient is not known. Congenital anomaly, post-inflammatory or post-traumatic injuries may be possible causes. Our patient underwent laparotomy more than 30 yr ago without apparent complications. He also had pulmonary tuberculosis diagnosed and treated decades ago. Both of these may be possible causes of laryngeal web formation in this patient. Sputum culture for tuberculosis was negative.

Airway management of unsuspected laryngeal web is clinically the same as managing patients with subglottic stenosis. Different sizes of tracheal tube should be available during induction of anaesthesia and the tracheal tube should not be advanced with force when resistance is encountered. Further traumatic injuries to the cords should be avoided as it may induce scarring and enhance web formation in the future, especially if both sides of the cords are injured. Web formation in the posterior commissures has been reported after intubation[8]: if this is encountered, it is best to awake the patient, postpone the operation and consult an otolaryngologist for evaluation of the airway anatomy. For emergency surgery, examination of the larynx with a flexible fibreoptic laryngoscope under local and topical anaesthesia before re-attempting intubation may minimize traumatic injuries to the vocal cords. Increased risk of laryngospasm, trauma and distressing iatrogenic airway obstruction while participating in awake fibreoptic laryngoscopy should always be borne in mind. Anaesthesia via a laryngeal mask, which is not traumatic to the vocal cords, would be an alternative choice. Another important point is postoperative follow-up of the patient as local bleeding, oedema and further formation of web may occur. The patient should be warned of these complications and the condition should be mentioned to the surgeon and anaesthetist if surgery is contemplated in the future.

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EQUIPMENT

Laboratory evaluation of the I-NOvent nitric oxide delivery device

J. D. YOUNG, M. ROBERTS AND L. B. GALE

Summary

The "I-NOvent delivery system" (Ohmeda Inc., Madison, WI, USA) is a device designed to add nitric oxide to a ventilator breathing system so that the inspired nitric oxide concentration remains constant in spite of changes in minute ventilation. In a laboratory study the device maintained the inspired nitric oxide concentration delivered to a model lung in the range 10.2–10.7 parts per million (ppm) when set to deliver 10 ppm, and in the range 40.5–42 ppm when set to deliver 40 ppm, for tidal volumes of 500, 700 and 900 ml, ventilator rates of 10, 15 and 20 bpm, peak inspiratory flow rates of 30, 40 and 50 litre min^{-1}, and square, sine and decelerating ramp flow waveforms. (*Br. J. Anaesth.* 1997; **79**: 398–401).

Key words
Pharmacology, nitric oxide. Equipment, breathing systems.

Inhaled nitric oxide is used increasingly to treat hypoxaemia and pulmonary hypertension associated with acute respiratory failure. Most centres in the UK use systems where a continuous flow of nitric oxide–nitrogen mixture is introduced into the inspiratory limb of the ventilator system, but this results in uneven nitric oxide concentrations being delivered during inspiration, and the inspired concentration changes when the patient's minute volume changes. There are only a few systems available for mixing nitric oxide with the inspired gas delivered by a ventilator which maintain a fixed inspired nitric oxide concentration in the face of varying minute ventilation. Two systems are available which only function with specific ventilators, the Nomius "C" for Siemens Servo 900 series ventilators, and the NODomo, for Dräger ventilators. True universal nitric oxide delivery systems, which can work with a range of ventilators or anaesthetic machines to deliver a fixed concentration of nitric oxide independent of minute ventilation or fresh gas flow, have not been available commercially. While we were constructing a prototype device[1] based on a fast-responding mass flow controller, we were aware that Ohmeda were independently developing a more sophisticated device (I-NOvent delivery system) using a similar principle. We report a bench test of the pre-production UK specification prototype of this device.

Description of the I-NOvent delivery system

The I-NOvent delivery system is shown in figure 1 and a diagram of the system is presented in figure 2. The device is mounted on a wheeled plinth which also acts as a carrier for two 10-litre nitric oxide–nitrogen mixture cylinders. Two regulators to reduce cylinder pressure to a lower working pressure are built into the plinth, together with two cylinder pressure (contents) gauges. The device measures inspiratory gas flow with a hot film anemometer placed in the inspiratory limb of the breathing system and delivers the appropriate flow of nitric oxide–nitrogen mixture (1000 ppm of nitric oxide in nitrogen) downstream of the flow sensor with an injector port integral to the sensor housing. The flow of the nitric oxide–nitrogen mixture is controlled with two proportional solenoid valves and monitored with hot film anemometers, effectively forming two

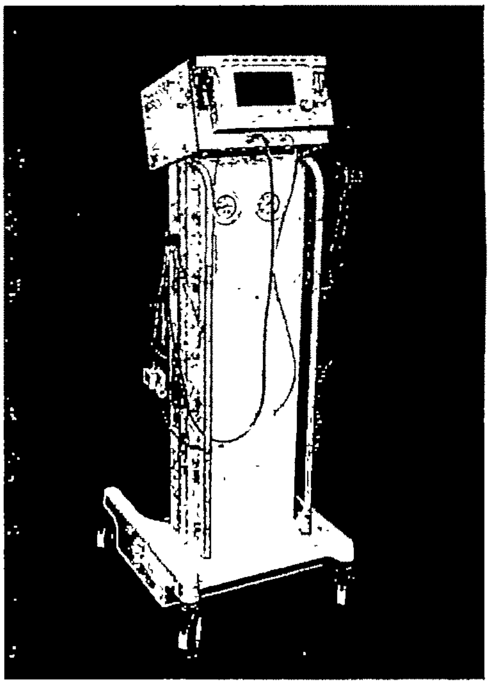

Figure 1 The I-NOvent delivery system.

J. D. YOUNG, BM, FRCA, DM, L. B. GALE, Nuffield Department of Anaesthetics, Radcliffe Infirmary, Woodstock Road, Oxford OX2 6HE. M. ROBERTS, BM, BCH, MA, FRCA, Anaesthetics Department, Royal Hospital Haslar, Gosport, Hants PO12 2AA.
Accepted for publication: April 2, 1997.
Correspondence to J. D. Y.

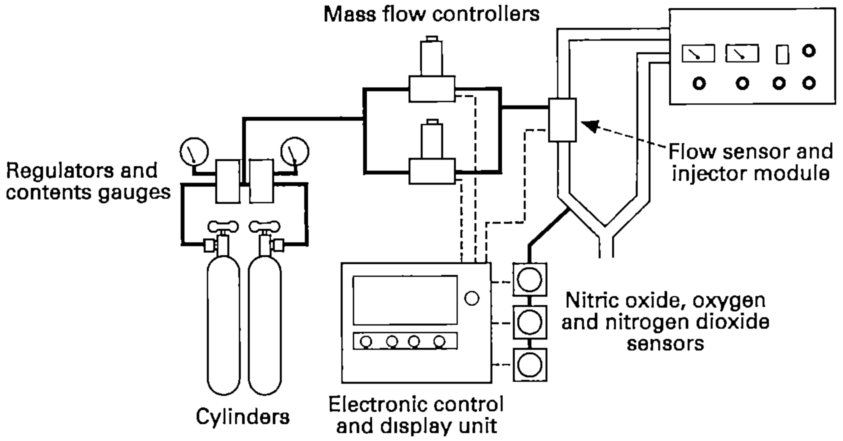
Mass flow controllers
Regulators and contents gauges
Flow sensor and injector module
Nitric oxide, oxygen and nitrogen dioxide sensors
Cylinders
Electronic control and display unit

Figure 2 Diagrammatic representation of the I-NOvent delivery system Heavy lines indicate the gas pathways; dashed lines indicate electrical connections. The manual ventilation system has been omitted for clarity.

mass flow controllers. Mass flow controllers are devices which control the mass rather than the velocity or volume of gas flowing through them. They are not affected by fluctuations in supply or downstream pressures. The mass of gas passing through can be controlled with an electrical signal. The inspired gas is sampled in the inspiratory limb of the ventilator system approximately 20 cm upstream from the Y piece of the system, and drawn through a water trap before being analysed for nitric oxide, nitrogen dioxide and oxygen concentrations by two electrochemical cells and a fuel cell, respectively. These sensors are for monitoring only, and do not have any effect on the control of nitric oxide delivery.

The front panel contains an electroluminescent screen on which measured inspired nitric oxide, nitrogen dioxide and oxygen concentrations are displayed. The set nitric oxide concentration is also displayed, together with any alarm messages. Calibration, alarms, delivered nitric oxide concentration and display brightness are controlled by seven multifunction push buttons and a single combined rotary/push switch control. The device can deliver nitric oxide 0–80 ppm at ventilator peak inspiratory flow rates below 55 litre min^{-1} and 0–50 ppm at ventilator peak inspiratory flow rates of 55–120 litre min^{-1}.

To allow nitric oxide to be delivered during manual ventilation the device is designed to be fitted with an external oxygen flowmeter, valve and inlet hose. If oxygen is turned on at 15 litre min^{-1}, nitric oxide is added to give a final concentration of 10 ppm. The oxygen–nitric oxide mixture then passes to an outlet which can be connected to a manual ventilation system. The manual system is totally pneumatic and independent of the primary system, and operates even if all power is lost to the device. A battery provides 30 min of backup power.

Test procedure

A Puritan Bennett 7200 ventilator (Puritan Bennett, Hounslow, UK) was used to ventilate a test lung (Lung Ventilator Performance Analyser, BOC Medical, Harlow, UK) set to a compliance of 50 ml cm H_2O^{-1} (510 ml kPa^{-1}) and a flow resistance of 5 cm H_2O litre s^{-1} (0.49 kPa litre s^{-1}). A sampling port was fitted to the test lung, which allowed the concentration of nitric oxide to be measured using an Eco Physics CLD 700AL chemiluminescence analyser (Eco Physics, Dürnten, Switzerland). The flow sensor for the I-NOvent delivery system was placed in the inspiratory limb of the breathing system after the inspiratory filter, the sampling port was placed in the inspiratory limb 20 cm upstream from the "Y" piece.

Flow into and out of the test lung was measured using a TUBA ultrasonic flow measuring device (Transit-time Ultrasonic Breath Analyser, GHG Medical Electronics GMBH, Zürich, Switzerland)[2] and flow of the nitric oxide–nitrogen mixture from the I-NOvent delivery system was measured by inserting a locally made screen pneumotachograph into the delivery tube. Pressure changes across the pneumotachograph were measured using a Validyne 2–0–2 cm H_2O (0.2–0–0.2 kPa) pressure transducer/amplifier (Validyne Engineering Co, Northridge, CA, USA). Flow signals were recorded at 500 samples s^{-1} using locally written software running on a Viglen 386 personal computer (Viglen Ltd, Alperton, UK) and an AT-M10-16 analogue-to-digital converter (National Instruments Ltd, Newbury, UK).

The sequence of ventilator settings was the same as we used previously[1]; in all cases 50% oxygen was used. The tests were performed at nitric oxide settings of 10 and 40 ppm. The ventilator was then set at 10 bpm, peak flow 40 litre min^{-1}, tidal volume 700 ml, square wave profile, and the device tested with nitric oxide settings of 1, 5, 10, 20, 40, 60 and 80 ppm, which are the marked concentrations on the bar indicator that is used to set the nitric oxide concentration.

The integral sensors were calibrated according to the manufacturer's instructions using air as zero for nitric oxide and nitrogen dioxide and 21% standard for oxygen, and nitric oxide 81.5 ppm in nitrogen, nitrogen dioxide 10.4 ppm in nitrogen and 100% oxygen, respectively, as span gases. The calibration gases were supplied by the manufacturer. The chemiluminescence analyser was calibrated using a separate nitric oxide 5.0 ppm standard and checked with the 81.5 ppm standard. The chemiluminescence analyser (in the mode used) has

Table 1 Results are grouped by inspiratory flow waveform. Within each group changes from the base settings of 10 bpm, tidal volume 700 ml and peak inspiratory flow rate of 40 litre min^{-1} are shown in bold type

					NO 10 ppm		NO 40 ppm	
Waveform	Ventilator rate (bpm)	Tidal volume (ml)	Peak flow (litre min^{-1})	I:E ratio	Inspired NO (chemiluminescence, ppm)	Inspired NO (built-in sensor, ppm)	Inspired NO (chemiluminescence, ppm)	Inspired NO (built-in sensor, ppm)
Square	10	700	40	1:4.4	10.2	9.3	41	38
Square	10	700	**30**	1:3.2	10.2	9.2	41.5	38
Square	10	700	**50**	1:5.8	10.3	9.6	40.5	38
Square	10	**500**	40	1:6.5	10.7	9.4	41	38
Square	10	**900**	40	1:3.3	10.5	9.4	41	38
Square	**15**	700	40	1:2.6	10.5	9.6	41	38
Square	**20**	700	40	1:1.7	10.6	9.5	41.5	38
Sine	10	700	40	1:2.8	10.7	9.7	42	38
Sine	10	700	**30**	1:1.9	10.7	9.6	41.5	38
Sine	10	700	**50**	1:3.7	10.5	9.8	41	38
Sine	10	**500**	40	1:4.3	10.7	9.4	41.5	38
Sine	10	**900**	40	1:2	10.6	9.5	41.5	38
Sine	**15**	700	40	1:1.5	10.5	9.5	42	38
Sine	**20**	700	40	1:0.9	10.5	9.6	42	38
Ramp	10	700	40	1:2.2	10.6	9.4	42	38
Ramp	10	700	**30**	1:1.5	10.8	9.5	42	38
Ramp	10	700	**50**	1.2.8	10.6	9.5	42	38
Ramp	10	**500**	40	1:3.3	10.7	9.4	41.5	38
Ramp	10	**900**	40	1:1.5	10.6	9.5	42	38
Ramp	**15**	700	40	1:1.1	10.6	9.4	42	38
Ramp	**20**	700	40	1:0.6	10.5	9.3	42	38

Table 2 Measured inspired nitric oxide concentrations with the ventilator set at 10 bpm, tidal volume 700 ml and peak inspiratory flow rate of 40 litre min^{-1} over the full range of available nitric oxide settings

Nitric oxide setting on the I-NOvent delivery system (ppm)	Inspired NO (chemiluminescence, ppm)	Inspired NO (built-in sensor, ppm)
1	0.96	1.5
5	5.02	5
10	10	9.3
20	20.1	18
40	40.5	37
60	59.2	55
80	79.4	74

a display resolution of 0.01 ppm, but the results are given to the nearest 0.1 ppm for the 10-ppm tests and 0.5 ppm for the 40-ppm tests as the standard gas mixes against which the analyser was calibrated are prepared to 2% accuracy. The flow sensor for the nitric oxide mixture was tested for linearity and calibrated using a Timeter RT-200 (SLE Ltd, South Croydon, UK) as the standard, and 100% nitrogen as the test gas. The TUBA is self-calibrating, and corrects automatically for gas composition. Nitrogen dioxide concentrations were not recorded from the CLD 700AL because calibration standards have to be prepared in the same gas mixture as the measured gas, and it was not possible to do this accurately.

Results

A total of 42 different combinations of ventilator and nitric oxide settings were tested (table 1). Table 2 shows the results of the linearity test at nitric oxide concentrations of 1–80 ppm. Figures 3 and 4 show the ventilator flow waveforms and the nitric oxide flow waveforms, for the three different inspiratory waveforms tested and for nitric oxide concentrations of 10 and 40 ppm. As the ventilator and device valves opened and closed, transient spikes were observed on the nitric oxide–nitrogen flow trace,

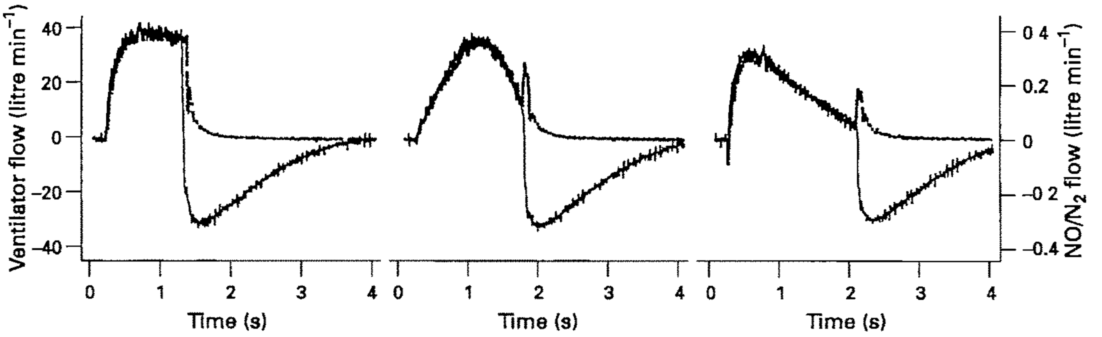

Figure 3 Gas flow measured at the "Y" piece of the ventilator (solid line) and flow of the nitric oxide–nitrogen mixture (broken line) during one ventilator cycle. Positive flow rates are inspiration. The three graphs are for ventilator settings of square, sine and ramp flow waveforms, respectively, with the I-NOvent delivery system set to deliver nitric oxide 10 ppm.

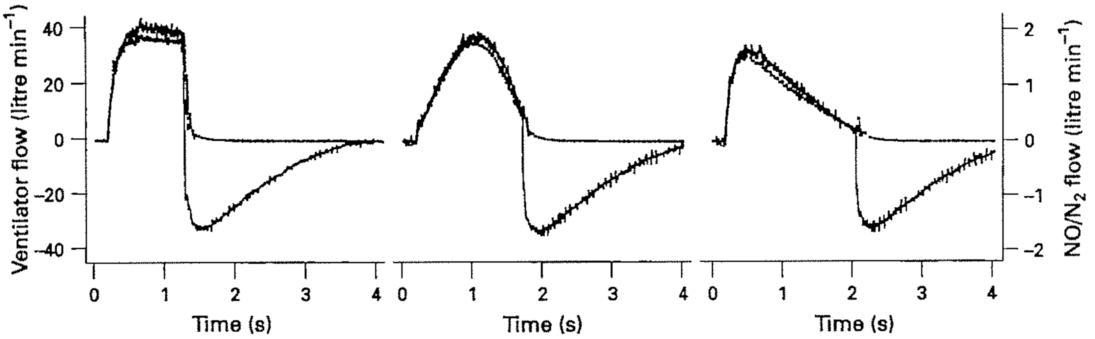

Figure 4 Gas flow measured at the "Y" piece of the ventilator (solid line) and flow of the nitric oxide–nitrogen mixture (broken line) during one ventilator cycle. Positive flow rates are inspiration. The three graphs are for ventilator settings of square, sine and ramp flow waveforms, respectively, with the I-NOvent delivery system set to deliver nitric oxide 40 ppm.

probably caused by the poor frequency response of the pneumotachograph. To partially remove these the nitric oxide–nitrogen flow traces were smoothed with a 41-point running average from the time the valve opened or closed to 80 ms later. The traces are otherwise unaltered.

Discussion

The device appeared to function very well. Control of inspired nitric oxide concentration over a wide range of ventilator settings was excellent, and more precise than is required in clinical use. Its ability to maintain constant nitric oxide concentrations over a range of settings was related presumably to the close matching of the ventilator and nitric oxide–nitrogen flow profiles, which were apparent on the flow traces. To achieve this the flow control devices (and their associated electronics) must have a very fast response time. Although we did not formally measure the response time of the device, the speed of response can be seen clearly on the flow traces at the start of inspiration, when the ventilator flow is changing rapidly. There was virtually no delay in the response of the delivery device.

The built-in nitric oxide meter consistently read lower than the chemiluminescence analyser except at 1 ppm, in spite of correct calibration, but the errors were small and not clinically important. In addition, the resolution of the electrochemical cells was only 1–2 ppm (3% of full scale), so the errors were within the expected range.

The limitations of these tests should be noted. They were conducted at a series of ventilator settings covering commonly used inspiratory flow rates, tidal volumes, rates and waveforms. However, we did not test the extremes of the ventilator capability (for example, the Puritan Bennett 7200 can deliver peak inspiratory flow rates of up to 120 litre min^{-1}), nor did we test the device in any patient-triggered mode (i.e. pressure support). We did not test the device with any continuous-flow ventilators or modes of ventilation, or paediatric ventilators. The absolute accuracy of any measured gas concentrations depends on the standards used, in this case they were within 2% of the nominal concentration.

The technology developed for this device may have other applications in respiratory physiology and experimental medicine. Sulphur hexafluoride injection into the inspiratory gas flow has been used to measure functional residual capacity, and sinusoidally varying concentrations of tracer gases added to the inspiratory gas flow can be used to determine deadspace, alveolar volume and pulmonary blood flow.[3] Until now it was very difficult to perform these measurements in patients undergoing ventilation because reliably adding and mixing tracer gases into the inspired gas is technically challenging. These techniques require careful matching of tracer gas flow to inspired gas flow, which is what this device is designed to do. Continuous measurement of lung volumes and pulmonary blood flow in patients undergoing artificial ventilation may be a useful spin-off from this project.

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COMMENTARY

Clinical evidence for delayed chloroform poisoning

C. M. THORPE AND A. A. SPENCE

Summary

From its introduction in 1847, chloroform proved to be a potent anaesthetic agent and over the next 50 yr its use became widespread. However, in 1912 the Committee on Anaesthesia of the American Medical Association stated that they were concerned with the occurrence of delayed chloroform poisoning in a number of cases. This conclusion was based on case reports and experimental animal data. However, subsequent studies and reported series of chloroform anaesthesia in humans have suggested a lower incidence of clinically significant liver injury. In this article we have investigated this discrepancy by analysing the published clinical data relating chloroform anaesthesia to liver damage. (*Br. J. Anaesth.* 1997; **79**: 402–409).

Key words
Anaesthetics volatile, chloroform. History, anaesthesia. History, chloroform.

James Young Simpson discovered the anaesthetic properties of chloroform in 1847[1] and introduced it into clinical practice in Edinburgh. He enthusiastically proclaimed it to be a superior drug to ether. Chloroform proved to be a potent anaesthetic agent and over the next 50 yr its use became widespread throughout the world. However, in 1912 the Committee on Anaesthesia of the American Medical Association pronounced that "The use of chloroform as the anaesthetic for major surgery is no longer justifiable".[2] They were concerned that "delayed chloroform poisoning occurred in a by no means inconsiderable number of cases". At this time, there were no accurate records of the incidence of delayed chloroform poisoning (DCP) and their conclusion was based on case reports backed by experimental animal data. However, subsequent studies and reported series of chloroform anaesthesia in humans have suggested a lower incidence of clinically significant liver injury. We were interested to explore this discrepancy by analysing the published clinical data relating chloroform anaesthesia to liver damage. Information may be divided into three groups: case reports of DCP, large series of chloroform administration and comparative studies.

Case reports

Sheehan published his experience of anaesthesia with chloroform in labouring women.[3] He noted that DCP occurred in patients with severe metabolic derangement after labours of 2–4 days or even longer, and he described the clinical course of illness: day 1: the patient is relatively well; day 2: vomiting occurs, with slight jaundice; day 3: the patient becomes seriously ill with restlessness, delirium, vomiting, upper abdominal pain, increasing jaundice and a low pyrexia; day 4: comatose with "characteristic groaning"; and day 5: deepening coma, increase in temperature and death.

Post-mortem histology showed mid-zonal or centrilobular necrosis of the liver. However, not all patients would develop the full syndrome and die. Davison's description of the clinical illness[4] concurred with Sheehan's account.

In many of the case reports before 1912 it can be seen that the course of illness did not fit that of hepatic damage (table 1). Therein lies one of the major problems of that time: DCP did not have a defined aetiology and clinical pattern. Because of this, a wide variety of causes of death after anaesthesia were attributed to a late poisonous effect of chloroform. Reading the case reports in table 1 it can be seen, for example, that Heyfelders' two cases[5] are convincing histories of liver failure, whereas others such as Guthrie's publications[9 11] indicate other diagnoses.

Bevan and Favill restricted the array of postoperative deaths attributed to chloroform by defining the underlying role of the liver in 1905.[15] They described late chloroform poisoning as a "hepatic toxaemia" causing vomiting, restlessness, fright, mild delirium, convulsions, coma, Cheyne–Stokes breathing, cyanosis and icterus in varying degree. They wrote that death usually ensued, and that fatty degeneration of the liver was seen post mortem. After their review, the term "delayed chloroform poisoning" (DCP) started to appear widely in the literature and the 1912 committee on anaesthesia equated DCP with necrosis of the liver.

C. M. THORPE*, MBBS, FRCA, A. A. SPENCE, CBE, MD, FRCA, FRCPED, FRCS, University Department of Anaesthesia, University of Edinburgh, Edinburgh Royal Infirmary, Lauriston Place, Edinburgh EH3 9YW. Accepted for publication: May 12, 1997.

*Address for correspondence: Anaesthetic Department, Gwynedd Hospital, Bangor, Gwynedd LL57 2PW.

We found 74 cases in the literature dating from before 1912. The evidence for death secondary to liver failure was very variable in these reports, with jaundice documented in only 20 cases. Frequently the finding of a fatty liver at post mortem was thought to be a sign of death secondary to DCP. In all, only 18 cases stand up to scrutiny as being potential instances of death secondary to liver failure, whereas 35 cases have clinical histories which suggest other causes of death. Twenty-one reports do not have enough information to determine if chloroform could have had an influence on the clinical course.

The case reports published after 1912 (table 2) have a higher proportion of patients with a clinical history compatible with liver failure. We found 49 case reports of patients with DCP in the literature, and 30 of these had documented jaundice. Eighteen patients had a history compatible with liver failure after chloroform anaesthesia, and only four patients had a history which suggested other pathology. In 27 of the 49 reports there was insufficient evidence to form a conclusion.

Large series (table 3)

The three large series published before 1912 had no documented reports of DCP. Snow,[42] Lawrie[45] and Neve[44] had records of 115 550 chloroform anaesthetics in total. Lawrie and Neve practised anaesthesia in India at the turn of the century. They stand out as having safe records of chloroform anaesthesia; however the nature of postoperative care at this time implied that follow-up of their patients was limited.

Between 1948 and 1970 several articles documented the incidence of hepatic damage after chloroform. Eleven authors documented a total of 310 274 chloroform anaesthetics. There were three deaths from liver failure and another six deaths in which it is unclear if the liver was involved. This gives an incidence of fatalities from liver failure of between 1 in 34 474 and 1 in 103 424. Three more patients with severe hepatic damage recovered. The incidence of documented jaundice was 1 in 10 342.

Comparative studies (table 4)

Nine studies comparing chloroform anaesthesia with control (usually halothane) did not show a clinically significant difference in liver damage. Orth[57] found detectable jaundice in six patients compared with three in the control group. However, numbers in these studies were small.

Discussion

Clearly the problem of liver damage after chloroform anaesthesia is not as great as was feared in 1912. A large number of case reports of DCP do not stand up to scrutiny. In many of these, the description is not that of hepatic failure and in those patients who have a reasonable history of liver damage it is difficult to implicate chloroform as the certain cause. However, it does seem reasonable to assume that there is at least some degree of hepatotoxicity in humans. The mechanism by which this may occur has not been elucidated fully, but it is thought to occur via active metabolites after hepatic metabolism of chloroform.[65] Hepatic chloroform degeneration proceeds by cytochrome p450-dependent oxidative pathways, producing reactive metabolites. These are prevented from covalently binding to microsomal proteins by hepatic glutathione (GSH). Phosgene, a reactive metabolite of chloroform, depletes hepatocellular glutathione.[61] The hepatotoxicity of chloroform may therefore be related to two factors: the rate of biotransformation of chloroform into its active metabolites and the availability of GSH to mop up these metabolites. Enzyme induction increasing the rate of metabolism may occur in association with barbiturates, alcohol and severe starvation, and this may explain the possible increase in hepatic damage with chloroform in patients with these conditions. A direct effect of chloroform on the hepatic microsomal calcium pump has also been suggested.[66]

Other causes of liver damage were prominent in the days of chloroform anaesthesia. Hypoxia and hypercapnia cause liver damage, irrespective of the anaesthetic agent used[58] and many anaesthetics were given in which the patient had a poor airway. The lack of supplementary oxygen compounded the problem and it is reasonable to assume that there were many hypoxic patients undergoing the knife. It is worth noting that the excellent safety records of Neve[44] and Lawrie[45] were achieved by anaesthetists who placed great importance on maintaining a clear airway.

In addition, the hepatic effects of chloroform are thought to occur more frequently in those patients with predisposing factors, such as hypoxia, hypercapnia, dehydration and acidosis, and alcoholism. There is no doubt that in the early years of anaesthesia these events were more likely to occur. The possibility of predisposition to liver damage was explored by Ballin in 1903.[12] He reviewed 10 cases of acute yellow atrophy of the liver, eight of which had been given chloroform. He made the point that in every case an inflammatory condition such as appendicitis was present and six of the cases were laparotomies. He thought that this predisposed the liver to the effects of chloroform, and also strongly inferred alcohol as a causative factor.

More recently, others have formed the conclusion that chloroform has had a rough deal. Davison, Wynn and Dykes[55] stated that chloroform was unlikely to produce damage to the liver when used in clinical doses for light anaesthesia. Dykes[67] pointed out that early workers were not successful in proving the existence or determining the incidence of DCP in humans. Davison[4] wrote that chloroform, administered by modern techniques, is no more dangerous than halothane. Strunin[43] analysed the evidence and concluded that chloroform did not entirely fit the criteria required for a drug to be classified as a hepatotoxin. Modern criteria for diagnosing drug-induced hepatotoxicity require stringent investigation. Factors that need to be taken into consideration are the temporal relationship of the disease to starting

Table 1 Case reports before 1912

Author	Date	Operation	Intraoperative course	Postoperative course	Jaundice?	Death	Post mortem
Heyfelder[5]	1847	1. Amputation	Severe cardiovascular depression	Restless, stupor, delirium	Yes	8 days	Nutmeg liver
		2. Amputation	No details	Restless, fever, delirium	Yes	8 days	No details
Casper[6,7]	1862	Amputation	No details	Never recovered senses	No	9 days	No details
Berend[6,7]	1850	1. Removal of shoulder blade	45 min. Stopped three times because of inky coloured blood	Vomiting, small volume, frequent pulse. Venesected	No	17 h	Fatty liver
		2. Amputation	Cried repeatedly on being cut	Generalized spasms	No	No details	No details
		3–10	Not described except for the inky colour of blood				
Bastinelli[7,8]	1890	3 cases	No details	Restlessness, vomiting. Jaundice in one case	Yes	3–10 days	Fatty changes, mostly central in one case
Guthrie[9]	1894	1. Vesical calculus	No details	Screaming, sweaty and cold, t=98F	No	10 h	Normal liver
		2. Aspiration of knee	No details	Screaming, vomiting and restless, t=103F	No	12 h	Pus in kidneys
		3. Genu valgum	1 h	Vomiting and delirium, t=102F	No	27 h	Liver pale and grey
		4. Tapiles equinovarus	Vomited twice	Vomiting, t=101F	No	30 h	Fatty infiltration of the liver
		5. Genu valgum	70 min	Vomiting, delirium, restlessness, coma, t=98F	No	53 h	Small liver
		6. Hydrocele	Took anaesthetic well. Long operation	Collapsed. Excessive vomiting, t=98.6F	No	24 h	Fatty infiltration
		7. Iliac abscess	Chloroform taken badly	Collapsed, vomiting, restless, delirious, t=104.6F	No	6 days	No PM
		8. Iliac abscess	Chloroform taken well. 15 min	Shocked 12 h after operation, t=99.2F	No	14 h	No apparent cause of death
		9. Double psoas abscess	1 h	Crying, vomiting, restless, flushed, t=103F	No	16 h	Fatty liver on section
Brewer[10]	1902	Gangrenous appendix	25 min	Delirium, paroxysms, respiration high, weak pulse, t=103C	No	4 days	Not done
Guthrie[11]	1903	1. TB of knee	None	Vomiting, urine output low, coma	No	3 days	Fatty liver
		2. Webbed fingers	Chloroform taken well	Vomiting, jaundice, unconsciousness	Yes	4 days	Fatty degeneration of the liver
		3. Shoulder naevus	20 min	Vomiting, restlessness, rapid pulse	No	28 h	No details
		4. Posterior pharyngeal abscess	10–15 min. Chloroform taken well	Vomiting, pyrexia, shivering. Became blue	No	33 h	No PM
Ballin[12]	1903	Appendix	25 min. Chloroform tolerated well	Vomiting, jaundice, restlessness, coma	Yes	Recovered	None
Montgomery[13]	1903	Inguinal hernia	Uncomplicated	Restlessness, coma	No	48 h	Liver buff colour
Stiles and McDonald[7]	1904	1. Inguinal hernia	20 min	Restlessness, vomiting, pyrexia, jaundice, rapid pulse and coma	Yes	3 days	Yellow fatty liver
		2. Genu valgum	22 min. Uneventful	Vomiting, restlessness, thirst, rapid pulse, cyanosis, coma, death	No	26 h	Yellow fatty liver. Pneumococcus in lung
		3. Perityphilitis	Necrotic tissue and pus in the abdomen	No details	No	9 days	Fatty degeneration, worse centrally
Steinthal[7]	1896	Fistula of caecum	2 h	Jaundice, rapid pulse, coma	Yes	5 days	No details
Salen and Wallace[7]	1899	1. Laparotomy for salpingo-oophritis	2 h	Jaundice, weakness, rapid pulse	Yes	3 days	Fatty degeneration of the liver
		2. Appendicectomy	No details	No details	No details	2 days	Fatty degeneration of liver, heart, kidneys
Dorner[7]	1899	Hernia	No details	Pyrexia, and "cardiac weakness"	No	42 h	Fatty changes in internal organs
Foerster[7]	1902	1. Osteotomy femurs	50 min	Cardiac weakness and vomiting (black vomit)	No	48 h	Extreme fatty change

Table 1 Case reports before 1912—*continued*

Author	Date	Operation	Intraoperative course	Postoperative course	Jaundice?	Death	Post mortem
Foerster		2. Appendix	No details	Restlessness, vomiting, jaundice, pyrexia, rapid pulse, coma	Yes	5 days	Yellow liver with fatty changes
Carmichael and Beattie[14]	1905	Osteotomy of the elbow	30 min	Restlessness, thirst, vomiting, coma	No	42 h	Enlarged yellow liver. Intense fatty change
Bevan and Favill[15]	1905	Gangrenous ovarian cyst	Prolonged induction and plenty of chloroform	Delirium, increasing pulse rate and temperature. Convulsions	No	110 h	Peritonitis. Fatty liver especially peripherally
Stocker[15]	1895	Strangulated ovarian cyst	No details	Restlessness, icterus, coma, death	Yes	No details	Acute yellow atrophy
Bandier[15]	1896	Incarcerated inguinal hernia	Anaesthesia easily produced	Delirium, jaundice, petechiae, haemorrhage, coma, t=40C	Yes	4 days	Acute yellow atrophy
Marthen[15]	1896	Dental extraction	40 min	Vomiting, restlessness, jaundice	Yes	3 days	Fatty degeneration of the liver
Cohn[15]	1902	Removal of uterine adnexae	Took chloroform well	Restless, vomiting, delirium, coma, jaundice. Pulse 150	Yes	4 days	Icteric nutmeg liver
Erlagh[15 16]	1895	Extirpation of uterus	Bilroths mixture	Icterus, delirium	Yes	No details	Acute yellow atrophy
Thiem and Fischer[7 15]	1890	Removal of blood from knee joint	No details	No details	No details	4 days	Fatty degeneration of the liver
Fraenkel[15 17]	1892	5 cases	2–4 h	No details	No details	40 h–20 days	Fatty changes in the liver in 4 cases
Telford and Falconer[18]	1906	1. Cleft palate	No details	Vomiting, increasing drowsiness, coma, t=102F	No	57 h	Liver canary yellow with fatty degeneration
		2. inguinal hernia	25 min. Chloroform not taken well	Collapse 1st day after operation. Vomiting coffee grounds. Became white and cold	No	1st day	Fatty degeneration in all organs
		3. Osteotomies femur and tibia	15 min	Rapid pulse, restlessness, decreased mental state. Briefly responded to 30 oz saline, then coma and death	No	60 h	Fatty degeneration of the liver
Thorp[19]	1908	Circumcision	Well taken, 7 min	Vomiting, rapid pulse, noisy respiration coma	No	37 h	Not done
Telford[20]	1908	1. Tuberculous	20 min	Vomiting, restlessness, rapid pulse and respiration. No urine output	No	40 h	Yellow liver. Extreme fatty change
		2. Genu valgum	25 min	Restlessness, vomiting, rapid pulse	No	2 days	Extreme fatty change
		3. Inguinal hernia	15 min. Straightforward	Vomiting coffee grounds. Melaena. Yellow tinge to skin	Yes	Recovered	
Bride[21]	1908	1. Tapiles	20 min	Vomiting coffee grounds, rapid pulse, coma	No	32 h	Pale yellow liver. Intense fatty change
		2. Genu valgum	15 min	Vomiting coffee grounds, abdominal pain	No	Recovered	
Wilson[22]	1908	Tuberculous hip	90 min	Nausea, thirst, apathy, restlessness haematemesis	Yes	8 days	Yellow liver with fatty infiltration
Taylor[23]	1908	Inguinal hernia	20 min. Uneventful	Restlessness, vomiting, rapid pulse, coma	No	38 h	Extremely fatty liver
Somerville[16]	1909	1. Genu valgum	ACE mixture	Vomiting, fast pulse and respiration, coma, slight yellowing of skin, t=106F	Yes	20 h	Not done
		2. Twisted ovarian cyst	No details	Vomiting, decreased urine output, rapid pulse, jaundice	Yes	60 h	Central necrosis peripheral fat
		3. Appendicitis	No details	Vomiting coffee grounds, jaundice, rapid pulse, collapse, t=102F	Yes	89 h	Central necrosis peripheral fat
Weir[24]	1909	Appendix 45 min	Uneventful	Restlessness, delirium, coma	No	Recovered	
Payne[25]	1909	3 cases of protracted vomiting.	No jaundice All recovered				
Whipple and Sperry[26]	1909	Incision and drainage chest wall abscesses	35 min. Good anaesthesia and recovery	Vomiting, delirium, restlessness, jaundice, rapid pulse and respiration	Yes	3 days	Extreme central necrosis of the liver
Telford[27]	1910	Pyloric stenosis	No details	Vomiting, restlessness, coma	No	4 days	Yellow liver, extreme fatty degeneration

Table 2 Case reports after 1912

Author	Date	Operation	Intraoperative course	Postoperative course	Jaundice?	Death	Post mortem
Fairlie[28]	1914	Laparotomy	38 min. Protracted induction	Vomiting, dullness, coma	No	77 h	Not done
Stander[29]	1924	Forceps	69 min	Drowsy, restlessness, vomiting, jaundice rapid pulse, cyanosis, t=102F	Yes	3 days	No details
Royston[30]	1925	1. Forceps. 108 h labour	No details	Jaundice, abdominal pain, vomiting	Yes	3 days	Centrilobular and mid-zone necrosis
		2. Craniotomy for fetal hydrocephalus (16 h labour)	No details	Jaundice, impaired consciousness, coma	Yes	Recovered	None
		3. EUA and delivery (24 h labour)	No details	"Abdomen much distended post delivery" Placental bleeding, vomiting, jaundice, coma	Yes	3 days	No details
Gilliat[31]	1928	No details	No details	"5 cases of delayed chloroform poisoning"	No details	No details	No details
Willcox[32]	1931	1. Forceps	No details	Restlessness, jaundice, coma	Yes	4 days	Central necrosis peripheral fat
		2. Appendix	No details	Drowsy, vomiting, jaundice, coma	Yes	5 days	Degeneration of liver cells and fatty degeneration
Stander[33]	1932	Second stage and repair of tear (2 day labour)	30 min	Increasing drowsiness and convulsion	No	3 days	Central necrosis of liver
Todd[34]	1934	Induction for disproportion	No details	Vomiting, drowsiness, rapid pulse coma? slight icterus after death	No	100 h	Central necrosis and fatty degeneration
Gibberd[35]	1935	1. Forceps (48 h labour)	35 min	Vomiting, jaundice, restlessness, coma rapid pulse, t=103F, convulsions	Yes	8 days	Central necrosis and peripheral fatty infiltration
		2. Forceps (30 h labour)	1 h	Jaundice, coma. Pulse 150, t=102F	Yes	5 days	Central necrosis fat peripherally
		3. Forceps	Two anaesthetics "a long time"	Drowsy, jaundice, coma, t=102.4F	Yes	6 days	Diffuse necrosis and peripheral fat
Grant and Miller[36]	1936	1. Manual rotation	30 min	Headache, fever, jaundice, coma, rapid pulse	Yes	7 days	Acute yellow atrophy
		2. Forceps	No details	Vomiting, jaundice. Resolved after 7 days	Yes	Recovered	
		3. Labour	Light chloroform	Developed scarlet fever after operation. Transient jaundice on day 5	Yes	Recovered	
Townsend[37]	1939	1. Forceps, 68 h labour	No details	Jaundice, vomiting, coma	Yes	2 days	Liver necrosis
		2. Second stage labour	No details	Vomiting, jaundice, coma, dilating pupils	Yes	Recovered	None
Sheehan[38]	1939	1. 4 patients with either hyperemesis or vomiting of late pregnancy		Died from either "clinical picture of DCP" and sepsis or from cerebral symptoms	Yes (presumed)	No details	2 gross centrilobular necrosis, 1 centrilobular fat, 1 fat throughout lobule
		2. 8 patients also quoted from other sources. Presumed to have had chloroform, however only documented in 2		No details	No details	No details	Centrilobular necrosis
Sheehan[39]	1940	1. 7 obstetric cases	No details	Jaundice from day 2	Yes	3–5 days	4 mid-zonal tending to centrilobular necrosis, 2 mid-zonal and centrilobular necrosis, 1 mid-zonal necrosis
		2. 2 cases termination for hyperemesis	No details	No details	No details	3–4 days	Centrilobular necrosis
Crawford[40]	1942	5 obstetric cases . All dehydrated and acidotic	No details	3 vomiting, jaundice, restlessness, delirium, 2 milder–just jaundice	Yes	Recovered	None
Marx and colleagues[41]	1962	Laminectomy	5.5 h. Severe blood loss and transfusion at one point	"In distress" followed by sudden stiffening and apnoea	No	2 days	Yellowish liver Mild centrilobular necrosis

Table 3 Large series of chloroform anaesthesia

Author	Date	Number	Incidents	Post mortem
Snow[42]	1858	4000	63 postoperative deaths. No documented jaundice or liver damage	No details
Neve[44]	1898	1. 15 843	2 deaths ?intraoperative. No mention of jaundice or DCP	No details
		2. 78 407	3 deaths, no details	No details
Lawrie[45]	1901	17 300	No mention of jaundice or DCP	
Middleton[46]	1948	1. 3000	As a Japanese prisoner of war. 1 patient with coma and death after 48 h	Acute yellow atrophy
		2. 4500	No fatalities secondary to the anaesthetic	
Gillespie[47]	1950	1111	10 patients with deranged liver function	Recovered
			1 patient died from bronchopneumonia	Fatty degeneration
Lenahan and Babbage[48]	1950	9724	No maternal deaths associated with anaesthesia	
Potter[48]		2500	2 deaths. No details	
Buerger and colleagues[49]	1955	1. 20 000	2 patients with toxic hepatitis	Recovered
		2. 129 530	1 death from delayed chloroform poisoning	No details
		3. 60 000	4 deaths but not specified whether liver involved	No details
Duncan and colleagues[50]	1956	18 302	1 death from fulminating pre-eclampsia. No jaundice	Peripheral necrosis in the liver
Dobkin and colleagues[51]	1960	154	5 patients with pre-existing jaundice. 4 patients developed jaundice:	
			a) 3 h gastrectomy. Developed jaundice and had tarry stool	Recovered
			b) Cholecystectomy. Previous jaundice. Subphrenic abscess and mild jaundice	Recovered
			c) Gastrectomy, Roux en Y. Bronchopneumonia and jaundice	Metastatic cancer Fatty degeneration of the liver
			d) Total colectomy. Transfused. Transient jaundice	Recovered
Siebecker and colleagues[52]	1960	1210	1 death from hepatic damage. Patient had 20–30 m of inadequate ventilation intraoperatively.	No details
Fote[53]	1960	1. 9669 Obstetric	Asymptomatic jaundice in 8 patients	
			1 patient with jaundice, lethargy, hypoglycaemia, convulsion and coma	Recovered
			1 patient with severe pre-eclampsia, pyelonephritis, septicaemia, jaundice and uremia	No details
		2. 199 Obstetric	1 patient developed jaundice	
Whitaker and Jones[54]	1965	1502	1 patient with transient jaundice. ? infectious hepatitis	
Davison[55]	1970	1. 1373	Follow-up limited but no suspicion of jaundice	
		2. 25 307	No liver damage	

Table 4 Comparative studies of chloroform anaesthesia

Author	Year	Study (patient numbers)	Results
Beesly[56]	1906	Chloroform (19) *vs* ether (24) *vs* mixture (3). All with appendicitis.	14 deaths with chloroform, 2 with "delayed poisoning". No jaundice. 2 deaths with ether. 1 death with the mixture of the two.
Orth[57]	1950	Chloroform (65) *vs* other (56)	Detectable jaundice in 6 chloroform patients and 3 "other" patients.
Sims and colleagues[58]	1951	Chloroform (38) *vs* ether (40)	No difference in hepatic injury between anaesthetic agents.
Bamforth and colleagues[59]	1960	Chloroform *vs* halothane (? 100 patients in total)	No liver injury in either group
Jones[60]	1963	Chloroform (29) *vs* halothane (32)	No complications with either group
McReynolds and colleagues[61]	1963	Chloroform (315) *vs* halothane (548)	No difference between groups. 1 patient with chronic liver disease died after 2 anaesthetics—one with each anaesthetic agent!
Griffiths and Ozguc[62]	1964	Chloroform (30) *vs* halothane (27)	No difference in liver enzyme changes
Oduntan[63]	1968	Chloroform (50) *vs* halothane (50)	No problems with either group
Smith and colleagues[64]	1973	Chloroform (58) *vs* halothane (42) *vs* regional anaesthesia (12)	No significant difference in liver function tests except BSP retention higher with chloroform

and stopping the drug, clinical pattern of the illness, epidemiological evidence, exclusion of other causes, assessment for pre-existing liver disease and the result of liver biopsies. Another investigation into causality, the re-challenge test, is too dangerous for routine use. These criteria were obviously not followed during the tarring of chloroform. Many other volatile agents have been implicated in liver damage. Their postulated idiosyncratic role in severe liver damage differs from the direct action proposed for chloroform and is discussed in detail by Ray and Drummond[68] and Elliot and Strunin.[69]

Modern anaesthesia provides accurate delivery of anaesthetic agents, and diligently monitors the airway and cardiovascular status. Given these accepted prerequisites for safe anaesthesia, chloroform does not have a high incidence of clinically significant hepatic damage. The incidence of hepatic failure after chloroform is between 1 in 25 800 and 1 in 51 700 and compares favourably with halothane, which is quoted as 1 in 35 000.[69]

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British Journal of Anaesthesia 1997; 79: 410–411

CORRESPONDENCE

Converting pH and H^+: a rule for the other thumb

Sir,—For some 80 yr, inappropriate adoption of Sørensen's pH nomenclature has obstructed ready understanding of biological acid–base relationships. Burden and McQuillan[1] are thus to be congratulated on their championship of the number 83 as an aid to overthrowing obfuscation. It is a pity that an unfortunately misplaced opening parenthesis might lessen the impact of their cunning observation (see erratum notice—editor (p. 413)).

May I try to assist transition to common sense with another observation? An approximation to the pH range of "normal" arterial blood is 7.45–7.35. These values happen to coincide with $[H^+]$ 35 and 45 nmol litre^{-1}, respectively. This coincidence may assist recollection of the nanomolar "normality" range.

Another property of the number 83 occurs to me: quite by chance, simple subtraction of the number 41 gives us the "answer to the great question of life, the universe and everything"[2] ... Silly? Not more so than an inverted scale of positive negative logarithms when simple arithmetic would suffice!

D. K. Girling
Department of Cardiothoracic Anaesthesia
Freeman Hospital
Newcastle upon Tyne

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MAC values of mixtures

Sir,—Sharpe and colleagues investigated the effect of desflurane and nitrous oxide anaesthesia on the auditory evoked response (AER), median frequency (F50) and spectral edge frequency (F95).[1] The investigators administered 1.5%, 3% and 6% concentrations of desflurane assuming that 6% desflurane=1 MAC. However, all of their patients received, at the same time, 66% (0.6 MAC) nitrous oxide. Let us assume that 66% nitrous oxide in oxygen=0.6 MAC[2] and 6% desflurane in oxygen=1 MAC.[3] Then, at each time the authors assessed changes in the AER, F50 and F95, the real potency of the anaesthetic mixtures (MAC values), corresponding to 1.5%, 3% and 6% desflurane, are those shown in table 1.

Table 1 MAC values of the anaesthetic mixtures administered

Anaesthetic mixture	MAC value
66% N_2O+6% desflurane	0.6+1=1.6
66% N_2O+3% desflurane	0.6+0.5=1.1
66% N_2O+1.5% desflurane	0.6+0.25=0.85

This highlights some flaws in the methodology of the study. In table 1 of Sharpe and colleagues' study, the authors noted: "Changes in variables for a 1 MAC change in desflurane ...". To which concentration of desflurane are they referring? If they mean 6% desflurane, the real MAC of the anaesthetic mixture is 1.6 MAC. If they are referring to the 1.1 MAC of the mixture, the actual concentration of desflurane in this anaesthetic mixture is 0.5%. For ages 31–65 yr, the addition of 60% nitrous oxide to desflurane reduces the MAC value of desflurane to 2.83%.[3]

It might be better if the authors had evaluated their results as changes in desflurane concentration with concomitant administration of 66% nitrous oxide and avoided the MAC concept. An alternative and perhaps correct presentation of their results might be to calculate the MAC of the anaesthetic mixtures and express these results in terms of MAC values of the mixture.

The MAC of a mixture is simply the sum of the MAC values of its components. The reason that 3% desflurane in 66% nitrous oxide is 1.1 MAC is that 0.5 MAC of the first and 0.6 MAC of the second anaesthetic are given. If more desflurane is given with the nitrous oxide concentration kept constant, the MAC value is increased at a rate of 1 MAC per 6% increase in desflurane concentration. In this study nitrous oxide contributed approximately 0.6 MAC, independent of the desflurane concentrations administered concomitantly.

Sharpe and colleagues found lower F50 and F95 values than those reported by Rampil and colleagues[4] at comparable concentrations of desflurane. However, to which concentrations of desflurane in Rampil and colleagues' study are they referring? In this study, desflurane 0.83, 1.24, 1.66 and 2.0 MAC multiples in oxygen were given to volunteers. Then, an equipotent mixture of desflurane–nitrous oxide was studied in which 60% nitrous oxide was substituted for 3% desflurane. The most likely explanation for the lower F50 and F95 values compared with those of Rampil and colleagues "at comparable desflurane concentrations" may be that the authors ignored the constant presence of nitrous oxide in their study, and the actual potency of the anaesthetic mixture (i.e. 0.85, 1.1 and 1.6 MAC values while administering 0.25, 0.5 and 1 MAC of desflurane, respectively).

One may argue that at equipotent concentrations nitrous oxide has much less effect on the AER compared with volatile agents.[5] Rampil and colleagues also showed that desflurane alone had a more pronounced effect on F50 and F95 than the equipotent desflurane–nitrous oxide mixture.[4] Nevertheless, it is incorrect and confusing to conclude for MAC values of volatile agents alone in the presence of nitrous oxide. The changes in potency in this case, by changing the volatile anaesthetic concentration and keeping constant the nitrous oxide concentration, were not linear.

Sharpe and colleagues claimed that they administered nitrous oxide for comparison with data from their previous studies. One might quantify the effect of 66% nitrous oxide and subtract this from the effect of volatile agent with nitrous oxide, provided that the effects of nitrous oxide on the AER, F50 and F95 are independent of the presence and concentration of the volatile anaesthetic. Another difference from the study of Rampil and colleagues is that Sharpe and co-workers studied patients, not volunteers. Were they studied during or before surgery, as the surgical stimulus may also affect AER, F50 and F95 changes in the opposite direction (less deep anaesthesia)?

A. Fassoulaki
Department of Anaesthesia
St Savas Hospital
Athens, Greece

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Sir,—Thank you for allowing us to reply to the concerns of Dr Fassoulaki regarding the MAC additive effect of nitrous oxide. The study aimed to investigate the effect of desflurane on the early cortical AER and the median frequency (F50) and spectral edge (F95) of the EEG. The presence of nitrous oxide was constant throughout and therefore any changes in the above variables were attributed to changes in the concentration of desflurane. It is clearly stated in the title and first sentence of the summary that nitrous oxide was given concomitantly.

The percentage change for each variable with changes in desflurane concentration was calculated from the regression slope of the measured variables. As it is assumed that the addition of nitrous oxide has a MAC additive effect (as pointed out by Dr Fassoulaki) this would simply change the position of the slope on the *Y*-axis and not the regression equation of the slope for a given change in desflurane concentration. We simply used a 6% change in desflurane concentration (equivalent to 1 MAC) for this calculation, so that a similar calculation could be made for equivalent potencies of other volatile agents such as sevoflurane.[1]

The lower median frequency (F50) and spectral edge frequency (F95) seen in our study compared with that of Rampil and colleagues[2] was not because we ignored the addition of nitrous oxide. Rampil and colleagues studied the EEG effects of desflurane in two groups; one with oxygen alone and the other with concomitant nitrous oxide. We compared our data with those of Rampil and colleagues in the nitrous oxide group. For example, Rampil and co-workers demonstrated spectral edge frequencies of 17.1 and 10.6 Hz for 3% and 6% desflurane in nitrous oxide, respectively, whereas in our study the frequencies were 11.2 and 5.5 Hz for the same concentrations of desflurane in nitrous oxide. We have speculated that the lower values for F50 and F95 seen in our study were a result of either age differences or the morphine–atropine premedication given in our study.

To answer the final point, our study investigated patients anaesthetized before surgery to avoid any confounding effects of surgical stimulus which have been demonstrated previously by our group.[3]

R. M. SHARPE
D. NATHWANI
S. K. PAL
C. THORNTON
M. D. BRUNNER,
C. J. DORÉ
D. E. F. NEWTON
Department of Anaesthesia
Northwick Park Hospital
Harrow

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The expanding role of simulators in risk management

SIR,—We compliment Professor Spence for his thoughtful remarks in his recent editorial.[1] While we agree with him that "computer screen-based simulators (SBS) ...... are particularly useful for learning alone or at home because they are obviously relatively mobile" we must point out that, although our ACCESS[2] simulator was designed to be mobile and has frequently been moved from hospital to hospital, the need for a real anaesthetic machine, ventilator, operating table and full size manikin makes home use impossible.

Nevertheless, we propose that ACCESS, with its use of full size equipment and the need for the trainee to perform several procedures, for example defibrillation or intubation, makes it a true theatre-type simulator (TTS) and the first of its type to be used in the UK. Although ACCESS cannot compete in terms of technical sophistication with the American designed simulator located in Bristol, it has the advantage of 4 yr of training use in the UK, being within the budget of a single department of anaesthesia (£4000 capital cost *vs* many £100 000's for the Bristol system) and provides a system which can be operated by a single tutor in an existing operating theatre. Although simulations using ACCESS can include other members of staff, for example surgeons and nurses, we have always taken the view that few hospitals have sufficient spare staff to allow this to take place regularly. In view of the evidence that skills are lost within 6 months of training,[3] we feel that to be effective, simulation must be available on a regular (6 monthly perhaps) basis. Although high-fidelity simulators have recently made the headlines, they are too expensive to provide the "training for everyone" that is needed to make anaesthesia safer. While these systems are good for the egos of flagship departments, they are inaccessible to most anaesthetists on a regular basis.

We agree fully with Professor Spence's comments on the use of simulators in assessing the adequacy of a doctor's clinical performance and endorse his view that "to turn away from simulators, or ignore an aspect which obviously some doctors would see as a threat, is not an option". We propose that an anaesthetic simulator such as ACCESS is so reliable and inexpensive that it can be provided in almost every anaesthetic department. Furthermore, we foresee the inclusion of such a simulator as part of Continuing Medical Education.

A. J. BYRNE
J. GARETH JONES
Department of Anaesthesia
Addenbrooke's Hospital
Cambridge

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British Journal of Anaesthesia 1997; 79: 412–413

BOOK REVIEWS

Clinical Anaesthesia. C.L. GWINNUTT. Published by Blackwell Science, Oxford Pp. 378; indexed; illustrated. Price £18.50.

This book aims to provide a comprehensive introduction to the specialty of anaesthesia for medical students and trainee theatre staff. In this it succeeds admirably, filling a gap between long established but dated anaesthetic texts aimed at the student, and the more comprehensive specialist textbooks.

The book is divided into five sections covering general anaesthesia, local and regional anaesthesia, intensive care, chronic pain and cardiopulmonary resuscitation. The section on general anaesthesia is further divided into 12 chapters concerning the conduct of anaesthesia from preoperative assessment to postoperative care. In between the author reviews such subjects as anaesthetic pharmacology, equipment and monitoring. The final section on resuscitation is to be commended and should be mandatory reading for all students before qualification.

All sections of the book are illustrated comprehensively with photographs and line drawings. Important principles are highlighted in text boxes. There is a comprehensive index and each chapter has a further reading list for the interested student.

I have shown this book to several medical students and trainee operating department practitioners; all have rated it highly. Their only reservation has been the price. This is a minor criticism and I would recommend this book to any interested student and indeed to their teachers.

I. McLaren

Textbook of Neuroanesthesia with Neuosurgical and Neuroscience Perspectives. M. S. ALBIN (editor). Published by McGraw-Hill, New York. Pp 1433; indexed; illustrated. Price £122.00.

The editor of this book is a well known senior neuroanaesthetist in North America, and he has invited a team of 76 co-authors, mainly from North America but not exclusively so, to make contributions. The list of authors resembles an edition of "who's who" in neuroanaesthesia. They have produced a very large and highly informative textbook: there are 1433 A4 pages and therefore this is more a reference volume than a handbook.

There are 38 chapters and it was difficult to note any plan in their order. After an interesting first chapter describing the history of neuroanaesthesia, there follows two detailed and informative chapters discussing cerebral blood flow and metabolism, cerebral oedema, intracranial hypertension and intracranial pressure measurement. Three chapters later there is a group of chapters describing monitoring of the brain. After another 10 chapters, which are individual essays on selected topics, there is a section of three chapters related to epilepsy. This is followed by a chapter on stereotactic surgery and then one on electroconvulsive therapy. The book continues in this style with the chapter on paediatric neuroanaesthesia lying between management of acute head injury and neurological intensive care.

Many chapters open with a full discussion of the surgical and medical management of the relevant pathology before discussing the anaesthetic management of the patient. This gives interesting background information, but would probably be of more use to neurosurgeons or neurologists. The title of the book does, however, indicate that this will be a feature of the volume. Discussion of anaesthetic management is obviously based on North American practice, but it is interesting to note the different anaesthetic techniques. Similarly, in the neuroradiology section there are detailed discussions of neuroradiology before there is any discussion of anaesthetic techniques and management of the patient.

I found the last chapter, which discusses brain death, vegetative state, donor management, and the cessation of therapy from an American point of view, very interesting. One difference is their use of atropine 0.04 mg kg^{-1} i.v. to see if there is any vagal activity which can be blocked. One reason for doing a confirmatory test such as EEG is if at least one of the basic tests was not performed by a neurologist, neurosurgeon or a critical care medicine specialist—neuroanaesthetists do not get a mention!

In addition to chapters dealing with topics which one would expect in a textbook of neuroanaesthesia, there are others on neurobehavioural evaluation, consciousness, delirium and coma, and physiological changes with ageing in the central nervous system.

Despite these criticisms, each chapter is detailed, the subject matter is discussed fully and there are large lists of references. The print is easy to read, the figures are clear and the book is well indexed. I doubt if it will be of value to candidates preparing for the Final Fellowship Examination, but I think it would provide interesting reading and a useful source of references in the library of a neuroanaesthetic department, or perhaps of the neuroscience unit as a whole.

J. L. Jenkinson

Anesthesia and Perioperative Care of the Combat Casualty. R. ZAJCHUK AND C. M. GRANDE (editors). Published by Office of the Surgeon General, United States Army Borden Institute, Walter Reed Army Medical Center, Washington. Pp. 946; indexed; illustrated.

This book is part IV of the *Textbook of Military Medicine* produced by the Office of the Surgeon General, United States Army. The project is a major undertaking and it would appear that the first volume in the series was published in 1989. My first criticism of the book is that it has taken a long time to produce. It is a big, heavy volume that will be appropriate on the shelves of a library. The task, set by the Editor-in-Chief, was to portray the entire expanse of modern combat casualty care. He rightly points out that there is a fundamental difference between combat casualty care in military medicine and trauma management in civilian hospitals.

The initial impression is that this book is well produced. There are 31 chapters to which more than 50 authors have contributed. But the result is a variation in style, repetition and glaring contradictions between chapters. The text is illustrated profusely but most of the truly anaesthetic illustrations have been reproduced with permission from other sources. Some of the illustrations are in black and white, others are in colour; on the whole they are clear and of good quality.

Evidence of how long this book took to produce can be found in the chapter on i.v. anaesthesia. This chapter is particularly disappointing, especially as the authors state that i.v. anaesthetic agents are for many reasons advantageous in the field. There is one reference to an article published in 1989 and none of the remaining 46 references is subsequent to that date. In the chapter on inhalation anaesthesia is the statement that trauma cases may be severely hypovolaemic and that anaesthesia may have to be induced with oxygen, neuromuscular blocking agents and hyoscine before the introduction of inhalation agents. Such statements did not fill this reviewer with confidence!

The American dilemma with anaesthetic machines for use in the field is well demonstrated. When the relevant chapter was written they had no anaesthesia machine with a field ventilator and for medico–legal reasons they were unable to use draw-over equipment in peace-time practice. They relied on full patient monitoring and the supply of compressed gases either from pipelines or cylinders. This was possible in the Gulf War, but is not always achievable near the front line, in Rwanda or Bosnia, for example, or wherever the next military response to aggression will be made.

As in any American textbook there are numerous references. Very few are from books or journals other than US publications. The largest number of references is in one of the intensive care chapters; 252 references which cover 12.5 pages! This particular chapter on syndromes of systemic inflammatory response and multiple organ dysfunction is well written but little is specific to military medicine. The references in the history chapter are particularly infuriating, for example "administration of gas and oxygen (23 references (pp. 649–650))".

Incidentally, reading the history chapter would give the impression that the Royal Army Medical Corps played a minor role in World War 1!

There are two British contributors to this volume, but this book is devoted to the American way; it will serve as an epitaph to US military practice. Much is already obsolete but at least it is recorded, so that lessons of the past do not have to be re-learnt in the future. This is not a pocket book and it is doubtful if a second edition will ever be published. It was conceived by surgeons and written by a heterogenous group of doctors as a major textbook. I fear that it will not be read by many outside the USA unless they are ardent followers of the American doctrine.

J. Restall

Thrombopoiesis and Thrombopoietins: Molecular, Cellular, Preclinical and Clinical Biology. D. J. KUTER, P. HUNT, W. SHERIDAN AND D. ZUKER-FRANKLIN (editors). Published by Humana Press, New Jersey. Pp. 412; indexed; illustrated. Price $150.00.

Over the past 15 yr, the isolation of erythropoietin, followed some time later by granulocyte–monocyte colony stimulating factor (GM-CSF) and granulocyte colony stimulating factor (G-CSF) and their commercial production by recombinant technology, have contributed significantly to the physician's armamentarium, particularly in the fields of nephrology and haematology. In the treatment of haematological and other malignancies, the ready, if expensive, availability of these granulopoietic growth factors, GM-CSF and G-CSF, has enabled new strategies in the chemotherapy of malignant bone marrow disorders, principally the escalation of drug doses with the aim of long-term palliation or cure. With the availability of molecular biology and recombinant manufacturing processes, it has always seemed inevitable that ultimately the third part of the therapeutic jigsaw would fall into place, namely the identification, isolation and commercial production of thrombopoietin, now believed to have a major role in the regulation of megakaryocytopoiesis and platelet production.

This book has, in addition to its four editors, two of whom have industrial backgrounds, one of whom is a scientist and one a physician, and two physicians, 33 other contributors, a small number of whom have scientific commercial roots. The volume is divided into six sections. The first deals with megakaryocyte and platelet physiology with asides into comparative haematology. The second describes in six chapters the history of the research for the physiological regulator of platelet production. The third section details the molecular biology of thrombopoietin, its gene and other transcription factors in megakaryocyte differentiation. The fourth section with five chapters deals with the cellular biology of megakaryocytes, platelets and other cytokines. Section five deals with the preclinical biology of thrombopoietin and finally a sixth part in two chapters deals with what is known of thrombopoietin in health and disease and the regulation of platelet production. It falls short of reporting clinical studies.

The book is well written, adequately illustrated and there is some overlap between chapters but, according to the editors, this has not been removed in order that alternative points of view might be expressed. This text encapsulates a determined search for the third physiological cytokine in haemopoiesis. It cannot be long before thrombopoietin is produced commercially, licensed and available for patients with serious blood disorders and other cancers, and one can foresee its important role developing, particularly in bone marrow transplantation.

J. K. Wood

ERRATUM

British Journal of Anaesthesia 1997; 78: 479.

The paragraph immediately below the table of Burden and Quillan's letter reads: "To convert pH from H^+, the numerical value of the two digits after the pH decimal point is calculated by subtracting H^+ from 83". The example given is $[H^+]=70.8$ nmol litre^{-1}.

Applying the conversion above:

$pH=7.(83-70.8)\approx 7.12$

and *NOT*

$pH=(7.83-70.8)$ as given, which equals -62.97.

We apologize to the authors for this, which arose during the editorial process.

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Dr J. M. Hunter,
Editor-in-Chief, *British Journal of Anaesthesia*,
University Department of Anaesthesia,
Royal Liverpool University Hospital,
The Duncan Building,
Daulby Street,
Liverpool L69 3GA.
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"I would have everie man write what he knowes and no more."—MONTAIGNE

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EDITORIAL I

Postoperative respiratory dysfunction: is the site of surgery crucial?

Upper abdominal surgery (UAS) is associated with significant impairment of respiratory mechanics, oxygenation, ventilation and pulmonary defence mechanisms, independent of general anaesthesia.[1] Changes in lung function in such cases are typically restrictive—rapid and shallow breathing, reduced forced vital capacity (FVC) and functional residual capacity (FRC) with consequent hypoxaemia. A shift from abdominal to rib cage breathing has been reported which has been attributed to loss of diaphragmatic contribution to tidal volume.[2] Proponents of upper abdominal laparoscopic surgical techniques have consistently claimed that, by avoiding an abdominal incision, postoperative pain is reduced and recovery of pulmonary function is expedited.[3,4]

In this issue, Joris, Kaba and Lamy describe a study which sought to differentiate the influence of site of surgery, parietal trauma, intraoperative patient position and pneumoperitoneum on pulmonary function and, by extension, to clarify their roles in the pathophysiology of postoperative pulmonary dysfunction.[5] The patient population was female, of normal body mass index and devoid of cardiopulmonary disease. The investigators chose to compare the effects of three types of laparoscopic surgery on effort-dependent measures of lung function, that is forced expiratory volume in 1 s (FEV$_1$), peak expiratory flow rate (PEFR) and vital capacity. Their hypothesis was that surgical trauma, rather than laparoscopy itself, is the primary determinant of postoperative pulmonary dysfunction.

A standardized anaesthetic and similar pneumoperitoneum conditions were used in the three surgical groups. However, inter-group differences in duration of pneumoperitoneum, sites of trocar insertion and patient position were unavoidable. Not expectedly, greater reductions in VC and FEV$_1$ were noted after upper abdominal laparoscopic cholecystectomy procedures. These changes were less than those usually associated with "open" cholecystectomy and the return to normal function was more rapid. Interestingly, there were no significant changes in VC, FEV$_1$ or PEFR after "minor" gynaecological laparoscopy. Pain scores were similar in the three surgical groups. Hence, the authors claim that the site of surgery is an important determinant of lung dysfunction after laparoscopy.

Joris, Kaba and Lamy have made valued and significant contributions to our understanding of the haemodynamic and neuroendocrine consequences of pneumoperitoneum during laparoscopic cholecystectomy.[6,7] This study confirms previous reports of reductions in expiratory lung volumes, FVC, FRC and arterial oxygen tensions after laparoscopic cholecystectomy.[8,9] However, the relevance of this particular study would have been enhanced by a larger sample size and a more comprehensive assessment of pulmonary function. When examining lung function after laparoscopy procedures, one might also consider changes in functional residual capacity (FRC), oxygenation and analgesic requirements.

In common with several other recent reports,[4,10] this study is concerned with maximum inspiratory and expiratory manoeuvres only. In 1973 Tahir and colleagues first suggested that upper abdominal surgery, and more precisely cholecystectomy, inhibits diaphragmatic function.[11] Subsequently, Ford and colleagues[12] demonstrated in 1983 that open cholecystectomy not only reduced maximum inspiratory and expiratory efforts but also modified spontaneous breathing patterns. The contribution of abdominal displacement to tidal volume (V_T) decreased relative to the thoracic component. They attributed these modifications to reflex inhibition of the diaphragm. Furthermore, they suggested that the origin of this diaphragmatic inhibition was afferent nociceptive impulses originating from the chest wall or the internal viscera, or both, after surgical trauma.

With the advent of upper abdominal endoscopic surgery, it was important to assess the impact of these new procedures, not only on maximum inspiratory and expiratory efforts, but also on respiratory patterns during quiet breathing, which are major determinants of gas exchange and may contribute to postoperative hypoxaemia. Couture and colleagues, in a study with significant implications for clinical practice, reported no significant shift from abdominal to thoracic respiration in 10 young patients after laparoscopic cholecystectomy.[13] Functional residual capacity and residual volume remained normal. The investigators concluded that diaphragmatic function remained intact during quiet breathing after laparoscopic cholecystectomy. If this is true, this study confirms the potential patient benefits compared with respiratory changes described previously after traditional "open" procedures.

Pneumoperitoneum creation *per se* might be expected to have adverse consequences for postoperative pulmonary function. The increased intra-abdominal pressure might produce cephalad diaphragm movement, compounding the reduction in FRC associated with general anaesthesia.

However, reassuring observations were reported after a study of seven patients undergoing diagnostic laparoscopy which did not find changes suggestive of diaphragmatic dysfunction.[14]

The site of surgery is a major determinant of postoperative respiratory dysfunction after upper abdominal surgery. The closer the incision to the diaphragm, the greater the reduction in postoperative lung volumes.[15 16] Kum and colleagues recently compared pulmonary function after "French" and "American" techniques of laparoscopic cholecystectomy.[17] There are fundamental differences in port placement in these two techniques. In the French approach, the surgeon stands between the patient's legs, with the ports being inserted in the mid-abdominal region. In the American technique, the surgeon stands to the left of the patient and the ports are concentrated in the right hypochondrium. Both groups were comparable in terms of anaesthetic technique, duration of surgery and degree of surgical trauma. Both FEV_1 and FVC at 6, 24 and 48 h after operation were better preserved in the American group. The authors concluded that the differences were in diaphragmatic dysfunction and in pain site, with similar total pain scores, but a higher location of the pain in the American group. The study by Joris, Kaba and Lamy supports the contention that the site of surgery is an important determinant of the magnitude of pulmonary dysfunction in laparoscopic and also open surgery.

While surgical trauma to the gallbladder is almost identical with open and laparoscopic techniques, it has been suggested that the advantages observed with the latter are related to the minimal trauma inflicted on the abdominal wall. One final caveat might be added; most studies have reported findings from relatively young and otherwise healthy populations. Similar observations after more extensive endoscopic procedures and in patient populations including the elderly, obese and those with co-existing chronic obstructive or restrictive airways disease would be reassuring.

H. McKeague
A. J. Cunningham
Department of Anaesthesia
Royal College of Surgeons in Ireland and
Beaumont Hospital
Dublin, Ireland

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EDITORIAL II

ORG 21465, a new water-soluble steroid hypnotic: more of the same or something different?

The first demonstration of the anaesthetic properties of steroid molecules was in 1927 when Cashin and Moravek produced hypnosis in cats using a colloidal suspension of cholesterol.[1] But it was not until the 1940s that a systematic review was undertaken by Selye into the hypnotic properties of steroids (mainly belonging to the pregnane and androstane groups).[2] Of the screened steroids, there was no apparent relationship between hypnotic (anaesthetic) and hormonal properties; indeed Selye found the most potent anaesthetic steroid to be 5β-pregnane-3,20-dione (pregnanedione), a metabolite of progesterone, that had little endocrinological activity.

Most steroid molecules are poorly water soluble, and little further development was seen until Laubach, P'An and Rudel synthesized hydroxydione in 1955[3] (fig. 1A). This was the 21-hydroxy derivative of 5β-pregnanedione, and was solubilized by esterification at the C_{21} position as the sodium hemisuccinate to give a somewhat unstable solution for i.v. injection. Studies in mice showed that hydroxydione had a high therapeutic index (17.3)[4] and few adverse effects in cats and dogs.[5]

In clinical practice hydroxydione produced minimal changes in cardiorespiratory function, good neuromuscular block, a low incidence of coughing and pleasant recovery, with a very low incidence of vomiting.[6 7] However, induction took several minutes. As there was early obtunding of the pharyngeal and laryngeal reflexes, it was possible to achieve airway intubation without the use of neuromuscular blocking agents. Hydroxydione was also a respiratory stimulant; the rate increasing with an accompanying decrease in tidal volume, leading to an increase in minute volume. Marked respiratory depression and apnoea were not usually seen. Cardiac output and systemic arterial pressure also decreased. There were, however, several unwanted side effects: pain on injection, high incidence of post-anaesthetic irritation at the site of i.v. administration and along the associated vein.

Studies by Robertson and Williams described the use of hydroxydione by continuous infusion.[8] Although they tried several approaches to overcome the thrombophlebitis (dilution of drug solution, premixing with blood, use of large veins), none achieved their goal. In their discussion, the authors surmised that some of the metabolites of hydroxydione might be responsible for part of its anaesthetic activity, particularly molecules with hydroxyl groups at the C_3 position (in place of the ketone) and at the C_{21} position (in place of the attached succinate moiety). This would, of course, have provided an explanation for the delayed onset of action of the steroid, and has been borne out by the more recent studies of Mok, Herschkowitz and Krieger in the mouse.[9]

Despite the limitations of hydroxydione, there has been a determined effort to seek other water-soluble steroid induction agents. Figdor and colleagues demonstrated anaesthetic properties of a series of water-soluble amino-esters based on 21-hydroxy-pregnanedione.[10] Further studies by Hewett and colleagues investigated the animal pharmacology of several androstanes or pregnanes with amino-radicals attached at C_2, C_6 or C_{16}.[11] The most potent in causing loss of righting reflex was 3α-hydroxy, 2β-morpholino, 5α-pregnan-20-one, which had a therapeutic index of 4.7. However, the compound had several disadvantages—long threshold time to onset of anaesthesia and a prolonged duration of effect. Introduction of an 11-keto group shortened the duration of the ED_{50} dose (30 to 17 min) but had little effect on potency.

A second line of investigation was undertaken by Phillips and colleagues who examined a range of steroids where basic side chains were added at

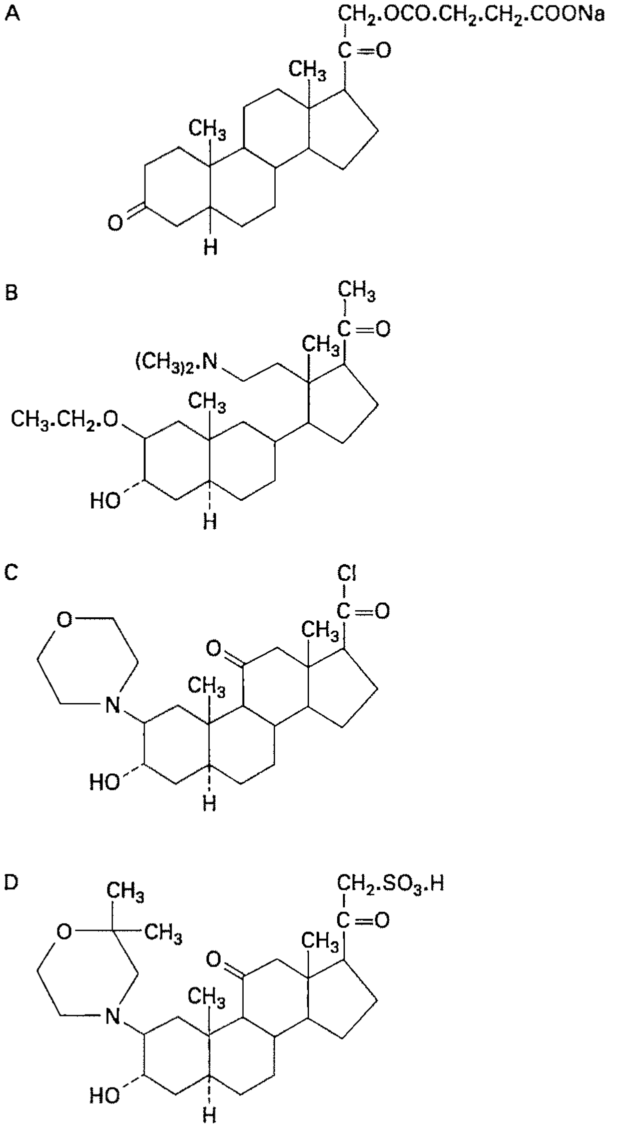

Figure 1 Structures of four water-soluble steroid hypnotic agents: A=hydroxydione; B=minaxolone; C=ORG 20599; and D=ORG 21465.

the C_{11} position.[12] Compounds with 11α or 11β-dialkylaminoacyloxy (or dialkylamino) substituents formed water soluble salts (usually the citrate) which showed anaesthetic activity in mice. Minaxolone citrate was one such steroid, where 11α-dimethyl amino and 2β-ethoxy groups were introduced into the pregnane ring, and the C_3 hydroxyl group was in the α-configuration (fig. 1B). Introduction of the 2β-ethoxy group led to increased potency compared with alphaxalone, while the dimethyl amino group at the C_{11} position in the C ring (in place of the dione group) conferred water solubility. In mice, cats and dogs, minaxolone had a high therapeutic index (>5) and was 2–3 times as potent as Althesin, and eight times as potent as thiopentone.[13] The properties of minaxolone and Althesin appeared similar—less respiratory depression and more rapid recovery than that seen after thiopentone, although there was greater incidence of excitatory movements during anaesthesia in dogs.

Clinical evaluation of minaxolone was carried out in 1251 patients between October 1978 and September 1979. Compared with Althesin, minaxolone had a slower onset of action and a more prolonged recovery.[14–17] The ED_{50} induction dose was 0.52 mg kg^{-1}.[15] When given by incremental dosing to supplement nitrous oxide, the incidence of excitatory movements and hypertonus were greater in patients receiving minaxolone than in the comparator group.[18] The cardiovascular and ventilatory effects of an induction dose of minaxolone 0.5 mg kg^{-1} were similar in magnitude to those after equipotent doses of Althesin.[16 19 20] Both steroids were associated with a low incidence of postoperative nausea and vomiting. When given by continuous infusion, minaxolone infusion rates of 10–15 μg kg^{-1} min^{-1} were needed to supplement 67% nitrous oxide in oxygen anaesthesia.[17] Comparison of the cardiovascular and respiratory effects with those of infusions of Althesin, propofol or methohexitone showed little difference between the four drugs.[21]

Unfortunately, delayed recovery after minaxolone was not its only adverse property. There was also a high incidence of excitatory side effects during induction, increased muscle tone during operation and involuntary movements during recovery, with an overall incidence of approximately 27%, but with a range of 18–45% depending on the premedication prescribed. The incidence of haemodynamic depression was low (3.9% overall), while comparative studies reported a lower incidence of ventilatory side effects than after other i.v. hypnotic agents with the possible exception of etomidate.[18]

Minaxolone also caused two more serious side effects—convulsions during recovery in three patients and abnormal liver function tests after prolonged infusion. In a subgroup of nine patients receiving minaxolone to supplement nitrous oxide for vascular surgery, there were no significant effects on hepatic function in seven of the subjects. However, the other two developed signs of postoperative obstructive jaundice (increases in alkaline phosphatase and serum bilirubin) in the first month after surgery.[22] The aetiology is uncertain, but the jaundice resolved spontaneously in both patients. In September 1979, minaxolone was withdrawn from clinical studies not for clinical reasons but because administration of large doses of the steroid (approximately 100 mg kg^{-1}) to a small number of rats was associated with CNS tumours. This was not supported subsequently by a larger toxicity study involving more than 600 animals.

More recently, two other water-soluble steroid hypnotic agents have been evaluated by Organon Ltd. In 1993, Gemmell and colleagues described the anaesthetic properties in the mouse, rat and dog of a water-soluble 2-morpholino substituted aminosteroid (ORG 20599)[23 24] (fig. 1C). In laboratory animals, this had an efficacy similar to that of Althesin, a high therapeutic index of 13 and was associated with an hypnotic effect of short duration. However, gross excitatory movements in animals, and problems relating to the stability and solubility of the methane sulphonate salt have prevented its evaluation in humans.

Another water-soluble aminosteroid has now been evaluated in both animals and humans (fig. 1D). ORG 21465 (as the base) showed a high therapeutic index of 13.8 compared with values of 4–5 for propofol and thiopentone.[25] In the monkey, ORG 21465 was compared with propofol in doses of 4 and 3 mg kg^{-1}, respectively. Both showed rapid onset of hypnosis, but duration of sleep and recovery was slower with the aminosteroid, while in the dog the effective hypnotic induction dose of ORG 21465 was 3 mg kg^{-1}, and maintenance doses were 2.8 μmol kg^{-1} min^{-1}, giving a potency ratio of 1:8 with respect to propofol. The early clinical data from human volunteers are presented in an article in this issue of the *British Journal of Anaesthesia*.[26]

Doses in excess of 1 mg kg^{-1} caused loss of consciousness within 1 min in unpremedicated male subjects, and the duration of effect was dose-dependent over the range 1.0–1.8 mg kg^{-1}. Preliminary kinetic data indicate rapid clearance from the blood (as we have reported previously for other steroids),[17] but there has been little evaluation of the kinetic–dynamic behaviour of the drug. As with other water-soluble steroids, the authors report a high incidence of excitatory side effects, although there was no accompanying EEG spike activity. Further clinical assessment of ORG 21465 in humans seems unlikely, and we are therefore left to wonder whether it is likely that any steroid anaesthetic agent will have a pharmacological profile superior to other i.v. induction agents presently available.

J. W. SEAR
Nuffield Department of Anaesthetics
University of Oxford
John Radcliffe Hospital
Headington
Oxford OX3 9DU

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British Journal of Anaesthesia 1997; 79: 420–421

EDITORIAL III

Meta-analysis: greater than the sum of its parts?

Evidence-based medicine, for physicians, patients and purchasers, is revolutionizing medicine in the late 20th century. While the fundamental principles are easy to grasp, much of the surrounding jargon can be confusing. Perhaps one of the most intimidating of all is the term "meta-analysis". The prefix *meta-* is defined by the *Shorter Oxford English Dictionary*[1] as "denoting a nature of higher order or more fundamental kind". Are we thus dealing with a highly complex technique understood only by the chosen few? The answer, of course, is no. Simply stated, meta-analysis is the process of quantitatively combining the results of several research studies on a particular topic to answer a specific question.

A conscientious practising clinician will regularly review the general and specialist literature in their field in order to ensure that the decisions they take and the care they give is the best available. Meta-analysis can be viewed as a systematic extension of this process of locating, assessing, interpreting and drawing conclusions from the ever-expanding body of research output. It is a secondary form of analysis of a set of primarily reported data, but it must still adhere to strict methodologies of approach to avoid the problems inherent in the combination of multiple studies. Rather than being a "vote" on a topic by simply counting studies for and against, the meta-analysis should aim to discriminate between, and weight studies, based on their power and quantitative result.

The following steps detail how a systematic review should be performed, but also highlights points whereby the discerning reader may appraise the validity of meta-analysis.

As with all research, the first step is to formulate the question. There must be a clear definition of the problem concerned and the "terms of reference" involved in order to identify what studies are relevant and qualify for inclusion in the overall analysis. This also aids the reader in later defining the contextual relevance of the meta-analysis to their own practice.

Systematic searching for all relevant research is essential. Computer searching of the common medical publication databases must be done in a structured way to ensure that all relevant articles are discovered. Automated searching can only be taken so far, however, and hand searching of the most relevant journals has been shown to detect many more articles than electronic searching.[2] Studies with negative or null findings are less likely to be written up, submitted or published than positive results, and thus it is vitally important not to restrict the review to published material.[3] A typical example may be the seeming ability of an anaesthetic agent to reduce the incidence of postoperative nausea and vomiting. A limited number of small weakly positive studies would seem to indicate a treatment effect. However, several adequately sized studies have illustrated a lack of effect. Were these to be included in a meta-analysis it would be apparent that there was no treatment effect. However, the publication bias results in only the positive studies reported and a spurious conclusion when these are considered in a systematic review. Consulting registers of clinical studies, large funding agencies and prominent researchers in the field are ways of ensuring that *all* relevant studies are considered.

Incentives are on hand to improve this process, most notably the Cochrane Collaboration[4] which exists to prepare, maintain and disseminate systematic reviews and meta-analyses. The Collaboration also co-ordinates and maintains a register of randomized, controlled studies, developed using electronic searching, hand searching of journals and conference proceedings, and from prospective study registries.

When as complete a set of reports of potentially relevant research studies as possible has been gathered, they must then be assessed for inclusion by strict criteria, ideally by using at least two referees to offset bias of interest.

(1) Studies should be randomized and controlled. Methods for combining observational comparison studies where the risk of bias is much higher are in their infancy, and at present the analysis of such data presents unresolved complexities that preclude acceptable presentation.

(2) There should be exact definitions of the treatments compared and the methods of comparison.

(3) Outcome data should be identified clearly.

(4) Each study should be assessed for any individual characteristics of its methodology that may influence and bias outcome. This may occur at any of four stages.

(a) Selection bias at study entry—when the randomizing clinician is aware of the treatment to which the next patient will be allocated and then excludes (possibly unconsciously), "unsuitable" patients.

(b) Performance bias—where two arms in a study are treated differently apart from the therapy or effect under study. For example, patients receiving opioids parenterally as opposed to orally, in a study of analgesic side effects are given other drugs i.v. also, which may induce hypotension when administered by that route.

(c) Exclusion and compliance bias—when subjects are non-compliant, lost to follow-up or excluded from analysis differentially between the treatment arms. For example, an active daily oral treatment may have substantial adverse side effects and lead to much lower compliance than a placebo control arm.

(d) Assessment bias—where outcome and effect are assessed by a researcher aware in some manner of group allocation, that is there has been a failure of observer "blinding". For example a new sedative given to patients in an ICU turns urine pink by virtue of a pharmaceutical congener effect which is absent from the control group.

Nurses involved in scoring sedation levels notice the difference.

Having selected the studies, the meta-analysis must then quantitatively combine estimates of effect, commonly given as either *odds ratios*, *relative risks* or *risk differences* for the risk of some event. Odds ratios are the most common measure of association, being a ratio of the odds of effect/non-effect in a treatment group compared with the odds in a control group. In low incidence events, this equals the relative risk, but where the incidence is higher the two measures diverge. An alternative means of summary description is the "number needed to treat (harm)". This is intuitively simple, just being the number of patients which would need to be given the active treatment in order to prevent (cause) a single adverse event. For example, for every 122 patients receiving a blood substitute, one will experience an anaphylactic reaction; the number needed to harm (NNH) is 122. Note that this figure is not of value in itself, but is for use in comparison with competing treatments for the same condition, and in a public health context between differing conditions.

One of the main questions (some would say dilemma) at the analysis stage is whether or not there is ***homogeneity of effect*** across the included studies. If so, a ***fixed effects model*** where the treatment effect is assumed to be ***constant*** is appropriate. Otherwise, a ***random effects model***, where the treatment effect can *vary* from study to study about an overall "average" effect is preferable. Whichever model is used, the final summary statistic is a measure of effect size and an associated confidence interval, with narrower intervals indicating increasing degrees of precision of results.

Obviously, conclusions made in the meta-analysis should be based on the data analysed and should not be coloured by the views of the authors. The key question that should be asked is "How universal are the results?" Did the review consider the treatment in all possible patients, or in a small subgroup? Were the effect sizes observed in the individual studies homogenous, and if not *why* not? Often similar studies compare therapies in patients at widely varying baseline risk, and it can be useful to plot the outcomes of the control group against the observed effect size. Is it reasonable to expect the treatment to have similar effects across all levels of risk?

Sensitivity analysis[5,6] is one method which can attempt to answer some of these problems. By including only randomized studies or studies on a particular subgroup of patients, the dependence of the conclusions on the assumptions made during the analysis (homogeneity of effect across all subgroups, similar populations, etc.) can be assessed. One example of this is the discrepancy sometimes observed between meta-analyses of the small studies and the large studies in the same area. Protocol variations frequently occur between centres and studies, in the real world. Meta-analyses that include a large number of small studies as opposed to a small number of large studies are more prone to such problems, which may lead to disagreements between overall similarly sized meta-analyses. Consider studies on the effect of extradural anaesthesia on the duration of the second stage of labour. Simple differences in obstetric practice between a large number of centres (e.g. the timing of vaginal examinations) may lead to wide variations in the accuracy of detection of the stages of labour in these small studies and significantly influence the end result. This effect may not occur in one or two large single centre studies, where consistent protocols of practice are in place. This is not to say that such multicentre reviews are flawed, merely that the results must be interpreted with these cautions in mind.

Finally, several authors have suggested that one of the most useful pieces of information to report about a meta-analysis is the total size of a study (or studies) which would need to be discovered in order to substantially change the conclusions of the meta-analysis.[7]

In conclusion, meta-analyses will never remove the need for large, multicentre, randomized, controlled studies. They are, however, invaluable for summarizing the often conflicting results of similar studies, and as part of the planning process for new research. Indeed, several major funding agencies now regard the completion of a systematic review of the evidence as a prerequisite stage in the planning of a randomized clinical study. Meta-analysis is not magic, however, and behind all the jargon is simply a research process. Good meta-analysis is founded on good science, and poorly conducted research studies cannot be fixed retrospectively. The onus is still on the primary researchers to design, conduct and report high quality studies and thus provide more grist for the meta-analysis mill.

M. J. SOUTER
University Department of Anaesthetics
Royal Infirmary of Edinburgh
Lauriston Place
Edinburgh EH3 9YW
D. F. SIGNORINI
University Department of Neurosciences
Western General Infirmary
Edinburgh

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CLINICAL INVESTIGATIONS

Postoperative spirometry after laparoscopy for lower abdominal or upper abdominal surgical procedures†

J. Joris, A. Kaba and M. Lamy

Summary

In this prospective study, we have compared women undergoing laparoscopic cholecystectomy, laparoscopic gynaecological surgery and laparoscopic minor gynaecological procedures (diagnostic, tubal ligation) (n=10 in each group) to determine if lower abdominal laparoscopy results in less postoperative pulmonary dysfunction than upper abdominal laparoscopy. Pulmonary testing was performed before operation, and 3 and 6 h after operation, on the first and second days after surgery. After operation, a significant reduction in forced vital capacity, forced expiratory volume in 1 s and peak expiratory flow rate occurred after laparoscopic cholecystectomy at each time. There were no significant changes after minor gynaecologic laparoscopy, whereas laparoscopic gynaecological surgery resulted in minor pulmonary dysfunction on the day of surgery only. We conclude that postoperative pulmonary function was less impaired after gynaecological laparoscopy than after laparoscopic cholecystectomy. This study suggests that the site of surgery is an important determinant of lung dysfunction after laparoscopy. (*Br. J. Anaesth.* 1997; **79**: 422–426).

Key words
Surgery, gynaecological. Surgery, laparoscopy. Lung, function.

Upper abdominal surgery performed via laparotomy is associated with postoperative respiratory changes, including a restrictive syndrome (reduced vital capacity and functional residual capacity), hypoxaemia, a change from abdominal to rib cage breathing and increased work of breathing. The site and size of incision,[1 2] postoperative pain[1 3] and diaphragmatic dysfunction[4–6] are the main factors contributing to the pathogenesis of these postoperative respiratory changes.

Laparoscopy, which avoids large abdominal incisions, allows a significant reduction in surgical trauma, postoperative pain and opioid requirements.[7–10] Laparoscopic cholecystectomy also results in less postoperative pulmonary dysfunction,[7 9–13] faster recovery of preoperative pulmonary function[12] and less atelectasis and hypoxaemia[11 12] than open cholecystectomy. Nevertheless, postoperative pulmonary dysfunction after laparoscopic cholecystectomy is significant. The role of inflammation of the punctured abdominal wall or gallbladder bed, or both, carbon dioxide pneumoperitoneum or intraoperative patient position in the pathogenesis of this pulmonary dysfunction is unknown. In all of these studies, pulmonary function was evaluated after laparoscopic cholecystectomy. Few data are available after lower abdominal surgical procedures, such as laparoscopic gynaecological surgery, or after minor laparoscopic procedures such as diagnostic laparoscopy or tubal ligation. Such data may be useful to differentiate the influences of the surgical site, parietal trauma, intraoperative position and pneumoperitoneum in the pathogenesis of pulmonary dysfunction.

Therefore, we have compared changes in pulmonary function after laparoscopy for cholecystectomy, gynaecological surgery and minor gynaecological procedures, such as diagnostic laparoscopy or tubal ligation.

Patients and methods

The study was conducted after obtaining approval from our institution's Ethics Committee and informed patient consent. We studied 30 consecutive women undergoing elective laparoscopic cholecystectomy (group Chol.), laparoscopic gynaecological surgery (group Gyn.) or laparoscopic minor gynaecological procedures (group Min.) (10 in each group). Inclusion criteria were body weight no more than 20% over ideal weight, age between 18 and 60 yr, absence of acute cholecystitis or pelvic inflammatory disease, and no cardiorespiratory disease or medications.

ANAESTHESIA

We used the same anaesthetic technique in all

Jean Joris*, MD, Abdourahmane Kaba, MD, Maurice Lamy, MD, Department of Anaesthesiology and Intensive Care Medicine, University Hospital of Liège, Belgium. Accepted for publication: April 12, 1997.

*Address for correspondence: Department of Anaesthesiology and Intensive Care Medicine, CHU of Liège, Domaine du Sart Tilman, B-4000 Liège, Belgium.

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This article is accompanied by Editorial I.

groups. All patients were given hydroxyzine 50 mg orally, 2 h before surgery, and an i.m. injection of midazolam 5 mg and atropine 0.25 mg before transfer to the operating theatre. Anaesthesia was induced with sufentanil 15 μg and propofol 2 mg kg^{-1}. After tracheal intubation facilitated by atracurium 0.5 mg kg^{-1}, general anaesthesia was maintained with isoflurane and 50% nitrous oxide in oxygen. Minute ventilation was controlled (Servo 900C, Siemens-Elema) and adjusted to maintain the end-tidal partial pressure of carbon dioxide at 4.0–5.0 kPa. During laparoscopy, intra-abdominal pressure was maintained automatically at 14 mm Hg by a carbon dioxide insufflator. At the end of surgery, residual neuromuscular block was antagonized with neostigmine 40 μg kg^{-1} and atropine 15 μg kg^{-1} i.v.

ANALGESIA

Pain intensity was measured using a 100-mm visual analogue scale at 3, 6 and 24 h after surgery. Treatment of postoperative pain was provided on the same nursing unit using a standardized regimen in all groups. During the first 24 h after operation, propacetamol 2 g, a precursor of paracetamol (Prodafalgan, UPSA Medica, Brussels, Belgium: propacetamol 2 g=paracetamol 1 g) were given i.v. every 6 h as necessary. If pain relief was considered inadequate (pain score >40 mm on a 100-mm visual analogue scale at rest) piritramide 0.2 mg kg^{-1} (Dipidolor, Janssen Pharmaceutica, Beerse, Belgium), a synthetic opioid, was administered i.m. On the second day, paracetamol 1 g with codeine phosphate 60 mg (Dafalgan codeine, UPSA Medica, Brussels, Belgium) were given orally at the patient's request every 6 h.

SURGERY

For all procedures, the laparoscope was introduced via a 10-mm diameter umbilical port. Laparoscopic cholecystectomies were performed using three additional trocars, one 10-mm and two 5-mm diameter ports, located in the right and left subcostal area, and the epigastric notch. For gynaecological laparoscopies, two trocars, one 10 mm and one 5 mm in diameter, were placed in the hypogastric region in addition to the umbilical port. Patients were tilted to the 10° head-up position for laparoscopic cholecystectomy and to the 20° head-down position for gynaecological laparoscopy. Care was taken to expel a maximum volume of gas from the abdominal cavity at the end of all laparoscopies.

PULMONARY FUNCTION

Pulmonary testing was performed in the sitting position by the same technician, who was unaware of the patient group, the day before surgery, and 3 and 6 h after surgery on days 1 and 2 after operation (except in group Min.; these patients were discharged on day 1). The following variables were recorded: forced vital capacity (FVC), forced expiratory volume in 1 s (FEV_1) and peak expiratory flow rate (PEFR). These variables were measured using a Microlab 3000 series bedside spirometer (Micro Medical Ltd, Rochester, England).

STATISTICAL ANALYSIS

Results are expressed as mean (SEM) except in table 1 where SD values are used. Data were analysed by analysis of variance followed by Scheffé's test for multiple comparisons. Results were considered to be statistically significant at the 5% level.

Results

Patient data and preoperative pulmonary function were similar in the three groups (table 1). In group Gyn., two patients underwent laparoscopically assisted vaginal hysterectomy, one had bilateral oophorectomy and the other seven had unilateral oophorectomy. In group Min., three women had diagnostic laparoscopy and the others had tubal ligation. Duration of pneumoperitoneum for cholecystectomy was significantly longer than for the other procedures, whereas duration of pneumoperitoneum in group Gyn. was longer than in group Min. (table 1). Pain intensity was similar in the three groups (table 2).

FVC, FEV_1 and PEFR did not change significantly after minor gynaecological laparoscopy. After laparoscopic gynaecological surgery, FVC and PEFR decreased significantly, but only on the day of surgery (19% and 29%, respectively), whereas no significant changes in FEV_1 were observed. After laparoscopic cholecystectomy, FVC, FEV_1 and PEFR decreased significantly at all times, except on day 2, when FEV_1 was no longer different than the preoperative value. In this last group, FVC, FEV_1 and PEFR reached their lowest values 3 h after

Table 1 Patient data and preoperative pulmonary function (mean (SD or range)) in those undergoing minor gynaecological laparoscopy (group Min.), laparoscopic gynaecological surgery (group Gyn.), or laparoscopic cholecystectomy (group Chol.) *=$P<0.05$ compared with group Min , †=$P<0.05$ compared with group Gyn

	Group Min	Group Gyn.	Group Chol
Age (yr)	39 (29–49)	40 (21–60)	39 (18–58)
Weight (kg)	59 (8)	61 (9)	64 (8)
Height (cm)	164 (4)	165 (3)	161 (5)
Duration of PNO (min)	17 (4)	35 (7)*	57 (20)*†
FVC (litre)	2.75 (0.49)	2.88 (0.49)	3.04 (0.51)
FEV_1 (litre s^{-1})	2.31 (0.39)	2.13 (0.57)	2.36 (0.40)
PEFR (litre min^{-1})	295 (88)	308 (95)	352 (92)

Table 2 Pain intensity (mean (SEM)) using a 100-mm visual analogue scale after minor gynaecological laparoscopy (group Min.), laparoscopic gynaecological surgery (group Gyn.), or laparoscopic cholecystectomy (group Chol.)

	+3 h	+6 h	+24 h
Group Min.	60 (7)	36 (10)	15 (2)
Group Gyn.	65 (5)	51 (9)	14 (6)
Group Chol.	52 (6)	40 (6)	18 (7)

surgery, and subsequently increased. The increase in FVC became significant relative to 3 h on day 1, and on day 2 for FEV_1. FVC, FEV_1 and PEFR were significantly lower in group Chol. than in the two other groups. FVC and FEV_1 in groups Min. and Gyn. did not differ significantly. PEFR in group Gyn. was significantly reduced compared with group Min. at 6 h after operation (figs 1–3). There were no correlations between duration of pneumoperitoneum and changes in FVC, FEV_1 or PEFR at any time.

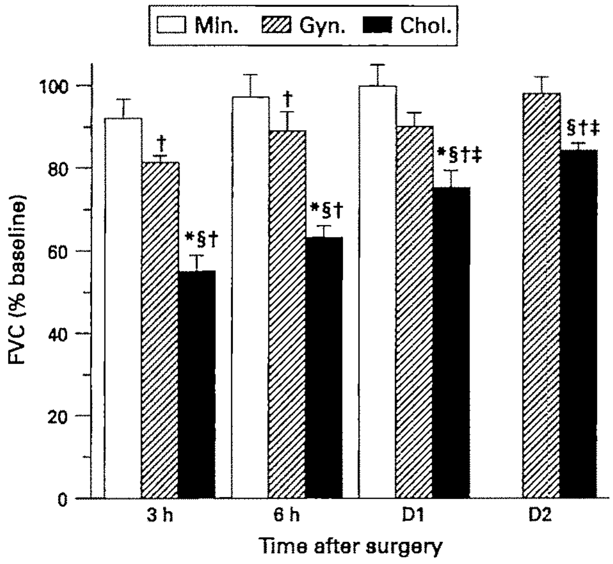

Figure 1 Changes in forced vital capacity (FVC) (mean (SEM)) after minor gynaecological laparoscopy (group Min.), laparoscopic gynaecological surgery (group Gyn.) and laparoscopic cholecystectomy (group Chol.). D1 and D2=Days 1 and 2 after operation. Significant differences ($P<0.05$) compared with: *group Min., §group Gyn., †before surgery, ‡3 h after surgery.

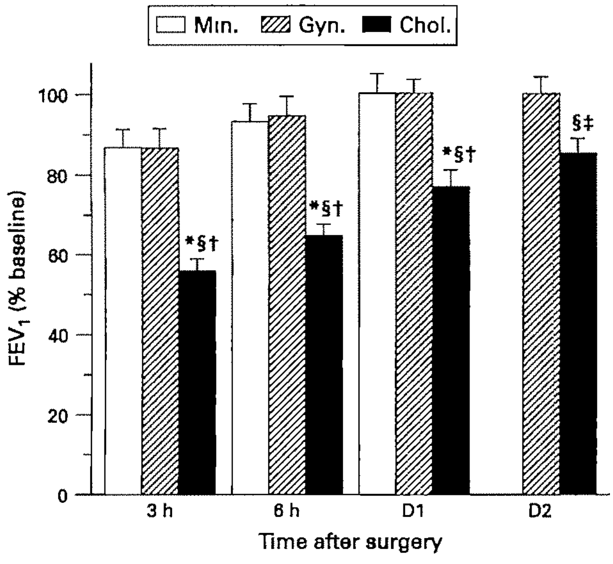

Figure 2 Changes in forced expiratory volume in 1 s (FEV_1) (mean (SEM)) after minor gynaecological laparoscopy (group Min.), laparoscopic gynaecological surgery (group Gyn.) and laparoscopic cholecystectomy (group Chol.). D1 and D2=Days 1 and 2 after operation. Significant differences ($P<0.05$) compared with: *group Min., §group Gyn., †before surgery, ‡3 h after surgery.

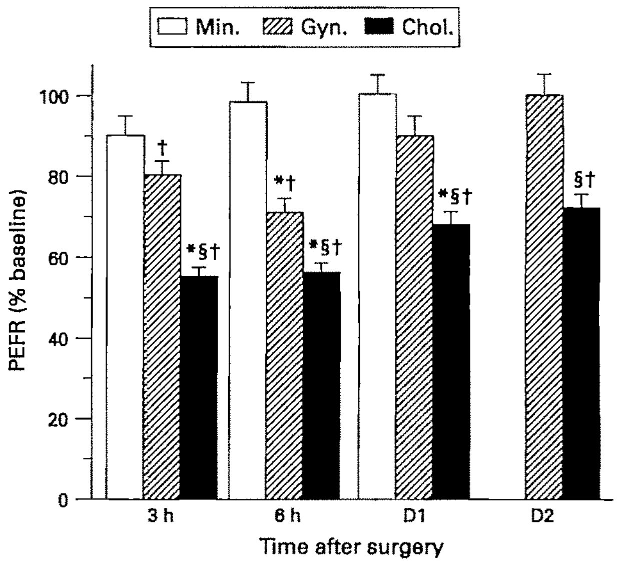

Figure 3 Changes in peak expiratory flow rate (PEFR) (mean (SEM)) after minor gynaecological laparoscopy (group Min.), laparoscopic gynaecological surgery (group Gyn.) and laparoscopic cholecystectomy (group Chol.). D1 and D2=Days 1 and 2 after operation. Significant differences ($P<0.05$) compared with: *group Min., §group Gyn., †before surgery.

Discussion

This study suggests that laparoscopy for lower abdominal surgery resulted in minor postoperative pulmonary dysfunction on the day of surgery only. Furthermore, these changes were less severe than those after upper abdominal laparoscopic surgery. Also, carbon dioxide pneumoperitoneum with minimal or no surgery, such as for diagnostic laparoscopy or tubal ligation, and Trendelenburg position did not produce significant changes in pulmonary function.

This study confirms the development of a restrictive pulmonary syndrome after laparoscopic cholecystectomy. Not only expiratory lung volumes,[7 9–13] but also functional residual capacity are reduced after laparoscopic cholecystectomy.[9 11 13] Postoperative atelectasis on chest x-ray, and decreases in Pa_{O_2} have also been reported.[11 12] In addition, changes in respiratory pattern, characterized by shallow breathing at a faster rate, were noted after laparoscopic cholecystectomy.[14 15] Therefore, although laparoscopic cholecystectomy is associated with better postoperative lung function than open cholecystectomy,[7 9–13] the patterns of alteration after cholecystectomy are qualitatively similar irrespective of the surgical approach. Consequently, the pathogenesis of pulmonary dysfunction observed after open and laparoscopic cholecystectomy should also be similar.

Pain contributes to impairment of pulmonary function after open upper abdominal surgery.[13] Several studies, however, failed to demonstrate clinically significant benefits (in term of improved rate of postoperative pulmonary complications) of extradural analgesia compared with conventional systemic opioid analgesia, despite better pain relief.[16 17] Similarly, extradural analgesia did not improve lung dysfunction after laparoscopic cholecystectomy.[18] Minor gynaecological laparoscopies are associated with a similar degree of trauma to the abdominal wall, as ports of similar sizes were used in these procedures. Moreover, laparoscopic tubal ligation, although considered to be a minor procedure, frequently results in severe pain.[19] Accordingly, similar pain intensities were reported by patients in the three groups. Nevertheless, in our study minor gynaecological laparoscopies resulted in no significant changes in pulmonary function. Similarly, laparoscopic hernia repair produces no postoperative ventilatory impairment although the same number of incisions are performed, in close proximity to the abdominal regions involved in laparoscopic cholecystectomy.[14] Therefore, pain, and more particularly incisional pain, does not seem to play a major role in the lung dysfunction noted after laparoscopy.

Whereas surgical trauma to the abdominal wall and the type of incision have been proposed as important causes of pulmonary dysfunction after open upper abdominal surgery,[1 2] Ford and colleagues showed that a reduction in diaphragmatic performance was the main determinant of impaired lung function.[4] Several clinical and experimental studies have suggested that diaphragmatic dysfunction possibly results more from reflex inhibition of efferent phrenic nerve activity secondary to irritation of splanchnic afferents, than from contractile failure of the diaphragm or surgical trauma to the abdominal wall.[4–6 20 21] After laparoscopic cholecystectomy, functional diaphragmatic impairment has also been documented.[14 15] Diaphragmatic electromyography using electrodes implanted in the diaphragm during surgery confirmed diaphragmatic dysfunction in the early postoperative period.[22 23] The magnitude of this dysfunction appears, nevertheless, to be less than that after open cholecystectomy.[15] Impairment of intrinsic diaphragmatic contractility after laparoscopic cholecystectomy has also been excluded.[14] Inflammation of the punctured parietal peritoneum, peritoneal inflammation secondary to carbon dioxide pneumoperitoneum, residual carbon dioxide accumulated under the diaphragm after operation and inhibitory reflexes arising from the gallbladder bed are all potential causes of diaphragmatic dysfunction after laparoscopic cholecystectomy. The lack of an effect of extradural analgesia on the restrictive syndrome after laparoscopic cholecystectomy excludes nociceptive abdominal stimuli as major determinants of diaphragmatic dysfunction.[18]

Moreover, in this study gynaecological laparoscopic surgery produced no or only minor postoperative pulmonary impairment despite similar trauma to the abdominal wall and a similar postoperative pain intensity compared with laparoscopic cholecystectomy. Although the extent of abdominal wall trauma was similar, the sites of trocar insertion were different for gynaecological laparoscopy and laparoscopic cholecystectomy, and might therefore contribute to differences in pulmonary function observed after these laparoscopic procedures. Nevertheless, Erice and colleagues did not observe diaphragmatic dysfunction after laparoscopic inguinal hernia repair, although sites for trocar insertion for laparoscopic hernia repair and cholecystectomy involved the same abdominal region.[14] These observations exclude parietal trauma as a possible source of inhibitory reflexes. The longer duration of pneumoperitoneum might be responsible for the more intense pulmonary dysfunction observed after laparoscopic cholecystectomy.[24] However, we did not observe a significant correlation between duration of pneumoperitoneum and any of the spirometric variables measured. The position of the patient may induce changes in lung volumes. Whereas the Trendelenburg position reduces functional residual capacity (FRC) and vital capacity in anaesthetized spontaneously breathing volunteers, the head-up position increases FRC.[25] Thus postoperative lung volumes might be expected to be affected more after laparoscopic procedures in the head-down position.[26] However, there were no significant changes in lung function in group Min. In addition, carbon dioxide pneumoperitoneum alone, such as for diagnostic laparoscopy, does not impair diaphragmatic function.[27] Accordingly, we did not observe pulmonary dysfunction in patients undergoing minor gynaecological laparoscopy. Therefore, the intra-abdominal site of surgery itself appears to be the main determinant of diaphragmatic inhibition after laparoscopic abdominal surgery,[14] as seen in open surgery.[28] The exact reflex neural pathways that cause this dysfunction need to be defined. Experimental data suggest that afferents for reflex inhibition of phrenic output possibly originate in the coeliac sympathetic plexus or other upper abdominal sympathetic ganglia.[20 21]

Taken together, these observations raise the question of the mechanism(s) accounting for the less severe lung dysfunction seen after laparoscopic cholecystectomy compared with open procedures. During laparoscopy, the most apparent reduction in surgical trauma results from the absence of large abdominal incisions. Consequently, postoperative pain, more particularly during mobilization and coughing, is less after laparoscopy.[29] Moreover, whereas incision of the abdominal wall results in persistent pain after laparotomy, pain after laparoscopy is more short-lived.[30] Finally, visceral pain accounts for most of the pain experienced after laparoscopic cholecystectomy, compared with parietal pain which is predominant after open cholecystectomy.[7] These changes in pain characteristics may explain why the contribution of incisional pain to the respiratory restrictive syndrome after laparoscopy is insignificant. Visceral trauma, the main determinant of postoperative diaphragmatic dysfunction, would be expected to be unchanged whatever the surgical approach. Nevertheless, handling and dissection of intra-abdominal viscera are more gentle during laparoscopy, probably leading to less visceral trauma. The consequent visceral inflammatory reaction might be reduced compared with open surgery. In support of this concept, it is notable that postoperative adhesions are less after laparoscopy compared with laparotomy.[31]

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Administration to humans of ORG 21465, a water soluble steroid i.v. anaesthetic agent

J. R. SNEYD, P. M. C. WRIGHT, M. CROSS, P. THOMPSON, G. VOORTMAN, M. M. WEIDEMAN, C. J. H. ANDREWS AND C. J. DANIELL

Summary

Ten male volunteers received a 1-min i.v. infusion of a new water soluble steroid anaesthetic agent, ORG 21465. Individuals received doses ranging from 0.8 to 1.8 mg kg^{-1}. All subjects experienced venous pain at the site of injection; those receiving 1.0 mg kg^{-1} or more became anaesthetized. There was no evidence of histamine release and apnoea did not occur. Excitatory phenomena were observed in all subjects and were dose related; no spikes were seen on the EEG. Pharmacokinetic analysis supported a three-compartment (non-weight-related) model with compartmental volumes V_1, V_2 and V_3 of 4.31, 14.2 and 89.4 litre, respectively. Clearance from the central compartment V_1 was 1.55 litre min^{-1}. Inter-compartmental clearances $\dot{Q}_1$ and $\dot{Q}_2$ were 2.54 and 1.79 litre min^{-1}. We found that ORG 21465 was an effective anaesthetic in humans. The relationship between sedation, anaesthesia and excitation requires further exploration. (*Br. J. Anaesth.* 1997; **79**: 427–432).

Key words

Anaesthetics i.v., steroid. Sedation. Pharmacology, ORG 21465. Pharmacokinetics, ORG 21465.

The anaesthetic properties of some steroids were described in animals in 1941 by Selye[1] and we now know that the likely mechanism of action is interaction at specific sites on the $GABA_A$ protein and the $GABA_A$ chloride channel complex.[2] Several different compounds of this type have been evaluated as anaesthetic agents in humans but problems with solubility, pain on injection and slow induction or recovery have often been a feature.[3 4] Some agents have reached clinical practice (notably minaxolone,[5] Althesin[6–8] and eltanolone[9–13]) but have subsequently been withdrawn because of toxicity problems.[14]

Recently, ORG 21465, a water soluble preparation of (2β, 3α, 5α)-3-hydroxy-2-(2,2-dimethylmorpholin-4-yl) pregnane-11,20-dione, has been identified as an anaesthetic and tested in some animal species (fig. 1). In voltage-clamped *Xenopus* oocytes expressing human recombinant $GABA_A$ receptors, ORG 21465 enhanced the inward current response evoked by GABA in a concentration-dependent and reversible manner.[15] The EC_{50} for this potentiation process was 2.3 μmol $litre^{-1}$; those for propofol and thiopentone are 2.2 and 3.8 μmol $litre^{-1}$, respectively. In preclinical testing, bolus injections of ORG 21465 were given to mice, rats, pigs and dogs. The dose required to produce sleep in mice was similar to that of other steroids. Mice given $2 \times ED_{50}$ doses of ORG 21465 slept for an average of 3.7 min; those given similar doses of alphaxalone, propofol and thiopentone slept for 1.7, 3.1 and 4.1 min, respectively.[15] The therapeutic index (LD_{50}/ED_{50}) of ORG 21465 for mice was 13, while those of alphaxalone, propofol and thiopentone were 23.7, 3.6 and 3.7, respectively.[15] In pigs and dogs, ORG 21465 acted as a potent, smooth, short duration anaesthetic.[15] We considered that ORG 21465 might be an effective and safe i.v. anaesthetic in humans and this study reports observations from the first 10 administrations to humans.

Subjects and methods

SCREENING AND PREPARATION OF SUBJECTS

We selected 10 healthy male volunteers, aged 22–28 yr, weighing 63–98 kg, after a preliminary screening process involving physical examination, treadmill exercise testing, echocardiography, haematological and biochemical screening. All subjects were within 15% of ideal weight for height and age, and had previously experienced general anaesthesia without incident. All subjects gave

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J. R. SNEYD, MD, FRCA, P. M C. WRIGHT*, MD, FFARCSI, M. CROSS†, MB, BCHIR, P THOMPSON†, RGN, G VOORTMAN‡, M M. WEIDEMAN§, PHARM D, C J. H. ANDREWS, PHD, FRCA, C. J DANIELL, FRCA, Department of Anaesthesia, Derriford Hospital, Derriford Road, Plymouth PL6 8DH UK. Accepted for publication. May 16, 1997.

*Department of Anaesthesia, University of Newcastle upon Tyne, NE1 4LP.

†Phase One Clinical Trials Unit, Tamar Science Park Derriford Road, Plymouth
PL6 8BQ.

‡NV Organon, Oss, The Netherlands

§Organon Teknika N V, Turnhout, Belgium.

Correspondence to J. R. S.

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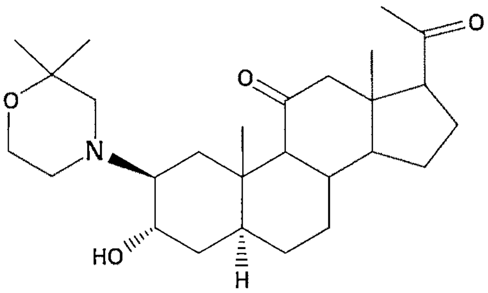

Figure 1 ORG 21465 is a water soluble preparation of (2β, 3α, 5α)-3-hydroxy-2-(2,2-dimethylmorpholin-4-yl) pregnane-11, 20-dione. Preclinical testing in mice, rats, dogs and monkeys indicated that ORG 21465 appeared safe and might be a suitable i.v. anaesthetic in humans.

written informed consent and the study was approved by the local Ethics Committee.

Subjects were admitted to hospital the night before drug administration and underwent another physical examination and urine screening for drug abuse or alcohol (Merck Triage kit). Subjects were starved from 22:00 and permitted to drink water until midnight. At 06:00 an infusion of Hartmann's solution at a rate of 3 ml kg^{-1} h^{-1} was commenced into the dominant forearm.

The study took place in a large room divided by a partition: the subject, two anaesthetists, an anaesthetist's assistant, a nurse taking blood samples and the camera operator were in one half of the room with essential anaesthetic and resuscitation equipment, and standard clinical monitors; observers, some technical staff and additional monitoring equipment were in the other half. This arrangement minimized the number of personnel and quantity of equipment in the immediate vicinity of the subject.

Additional cannulae for sampling arterial and venous blood were inserted in the non-dominant arm using local anaesthesia. Oxygen was administered by a single nasal cannula and a capnograph sampled airway gas from the contralateral nostril.

DRUG ADMINISTRATION

ORG 21465 was formulated in a buffered aqueous solution at a concentration of 20 mg ml^{-1}, pH 4. Each infusion of ORG 21465 was preceded by infusion of an equal volume of the buffered solution without ORG 21465 (inactive vehicle). After preparation, subjects rested quietly for a minimum of 20 min before administration of inactive vehicle, which took place close to 10:00. Another rest period of 10 min preceded infusion of ORG 21465. Both infusions were given into the dominant arm through the same cannula as the i.v. infusion over 60 s. Each subject received a single dose of ORG 21465 0.8, 1.0, 1.2, 1.5 or 1.8 mg kg^{-1}.

The first subject received 0.8 mg kg^{-1}, as this dose was predicted to be sub-anaesthetic in humans by extrapolation from animal data. Subsequent subjects received higher doses according to a dose escalation scheme, allowing consecutive subjects to receive larger doses until one subject became anaesthetized. When the first subject became anaesthetized, the next subject received the same dose; subsequently, dose increases were allowed provided that the previous subjects had been studied safely. Twenty-four hours after administration of the dose, biochemical and haematological data from each subject were reviewed before the next subject was studied.

MEASUREMENTS

Clinical observations

Clinical observations were made using two video cameras. One was located head high, at the foot of the bed, and monitored continuously the whole subject. A second, portable camera was used to document features of particular interest. All video images were time stamped. In addition, immediately after each subject was studied, an anaesthetist prepared a written summary of the subject's responses. Occurrence of the following observations were recorded and timed: pain on injection; loss of verbal contact; dropping a water-filled 20-ml syringe held between the thumb and forefinger of the supported dominant forearm, abducted approximately 30° from the supine subject; loss of eyelash reflex; and eye closure. During anaesthesia, at intervals of 30–60 s, subjects were called by their name and asked to open their eyes in order to determine their state of consciousness. Times to eye opening to direct verbal command, moving of limbs to direct command and recovery to a Ramsay sedation score[16] of 2 were noted. Evidence was sought of pain on injection, thrombophlebitis and any signs of excitation, including twitching, seizure, coughing, hyperreflexia or myoclonus.

Physiological measurements

Arterial pressure was measured directly until 90 min after administration of the dose when non-invasive methods were substituted and continued for 12 h. Heart rate was recorded for 12 h and cardiac index was estimated using bioimpedance (Bomed NCCOM 3) during the first hour after drug infusion.

Ventilatory frequency was monitored by nasal capnography. Adequacy of ventilation was judged empirically by the attending anaesthetist and supported by video recordings.

The EEG was recorded using a two-pair, five electrode system (Transmed TM-20). All electrode impedances were less than 10 kΩ.

Biochemical screening

Blood was obtained before the study and at 24 and 72 h after treatment. Concentrations of sodium, potassium, bicarbonate, urea, chloride, creatinine, total protein, albumin, bilirubin, creatinine phosphokinase, alanine transaminase, aspartate transaminase, gamma glutamyl transferase, alkaline phosphatase, glucose, calcium, phosphate, uric acid, cholesterol, triglycerides and acid glycoprotein were measured. Haemoglobin concentration, red blood cell variables, platelet count and differential white cell count were also measured.

Blood sampling and assay for ORG 21465

Arterial blood samples were obtained immediately before drug administration and at 0.5, 1, 2, 3, 4, 7, 10, 15, 20, 30, 45, 60, 120, 180 and 240 min after the start of drug infusion. An additional sample was obtained at the time of eye opening to command. When collecting samples, allowance was made for the cannula and three-way tap deadspace, estimated to be less than 0.2 ml, by withdrawing at least 0.5 ml before sampling. Samples (5 ml) were transferred to heparinized tubes, cooled and centrifuged within 1 h at 3000 rpm for 10 min. The separated serum was subsequently stored at −20 °C until analysis.

Extraction of ORG 21465 and internal standard (Org 1710, comparable with ORG 21465 but demethylated at the morpholinyl ring) from alkanized plasma was performed with n-hexane. Plasma concentrations of ORG 21465 were measured by capillary gas chromatography with mass-selective detection in the positive ion chemical ionization mode. Ammonia was used as the reactant gas. Capillary GC-MS was conducted on a Hewlett Packard 5890 series 11 gas chromatograph coupled directly to a Finnigan MAT SSQ mass spectrometer. The protonated molecular ion of ORG 21465 was monitored at m/z 446.1 and internal standard at m/z 404.1. Duplicate calibration samples (seven concentrations from 40 to 200 ng ml^{-1}), blank plasma samples and triplicate quality control (QC) samples of ORG 21465 in plasma at three concentrations (160, 400 and 1600 ng ml^{-1}) were included in every series of analyses. Per series of analyses, all samples of one or two subjects were measured. The inter-assay coefficient of variation (cv) was 11.2% at the low QC concentration. The intra-assay cv was 11.1% at the low QC concentration, 6.9% at the mid QC concentration and 4.7% at the high QC concentration. The accuracy of the assay, expressed as a deviation from the nominal spiked values (mean value/nominal value) of QC samples was 92.1% at the low QC concentration, 93.7% at the mid QC concentration and 99.9% at the high QC concentration. Results were mean values over nine analysis series. ORG 21465 is stable in human plasma for a period of at least 8 months. Repeated freezing and thawing does not influence ORG 21465 concentration.

PHARMACOKINETIC ANALYSIS

All pharmacokinetic analyses were performed using an iterative non-linear modelling program, NONMEM version IV,[17] on a Hewlett Packard series 9000/710 workstation. Mixed effects pharmacokinetic population models were fitted to the arterial drug concentration data. The mixed effects approach defines a single basic model of typical values (population means) for the pharmacokinetic variables. Variations in each individual from the basic model are defined by the use of a variable number of additional, user defined "inter-individual variability" parameters, each defining a degree of variability in one or more of the basic parameters. For example, clearance (*Cl*) was modelled as:

$$Cl=Cl_{typical}\times\exp(\eta)$$

where Cl=value for an individual, $Cl_{typical}$=typical value (mean) for the population, and η=normally distributed random variable with mean zero. Both the basic model and inter-individual variability can also be wholly or partially modelled as functions of physiological covariates, the aim being to reduce the residual degree of inter-individual variability. The basic variables of the models used here were volume of the central compartment (V_1), volume of the peripheral compartments (V_2 and V_3), clearance (Cl; elimination clearance=$V_1\times k_{10}$), fast distributional clearance ($\dot{Q}_1=V_1\times k_{12}$) and slow distributional clearance ($\dot{Q}_2=V_1\times k_{13}$). Volume of distribution at steady state (V^{ss}) is $V_1+V_2+V_3$. Population models were fitted using the first-order method of NONMEM with which the exponential error model illustrated earlier is equivalent to a constant coefficient of variability error model. Bayesian estimates of each individual's pharmacokinetic variables (for those where variability could be modelled) were then obtained using the *post hoc* step of NONMEM.

We first fitted individual two- and three-compartment models to the data from each individual. A three-compartment model was considered statistically justified if the −2 log likelihood (objective function) was more than 6 less then the reduced (two-compartment) model. The three-compartment model was justified in each case and therefore subsequent population base modelling was performed using a three-compartment model. We next built a population pharmacokinetic model, adding inter-individual variation parameters until no further modelled variation could be justified. The justification for each additional inter-individual variation parameters was for it to improve the goodness of fit statistic (−2 log likelihood) by >3.8 (evaluated against the chi-square distribution this is equivalent to significance at the 0.05 level), and to result in a visual improvement in the goodness of fit. Finally, using the same justification criteria we attempted to model each pharmacokinetic variable as a function of weight.

Results

We studied 10 male subjects, aged 22–34 yr, weighing 64–98 kg.

CHARACTERISTICS OF ANAESTHESIA

All subjects suffered discomfort on injection of both inactive vehicle and ORG 21465, with eight reporting pain. There were no cutaneous or cardiovascular signs of histamine release. The subject who received 0.8 mg kg^{-1} stopped speaking at 2.5 min but did not lose his eyelash reflex or drop the syringe. Anaesthesia was produced at all doses in excess of 0.8 mg kg^{-1} (table 1). The quality of induction was variable, with subjects who received 1.2 and 1.8 mg kg^{-1} displaying signs of airway irritation, notably coughing and sneezing. Induction of anaesthesia, as timed by syringe drop, took approximately 1 min

Table 1 Clinical responses to ORG 21465. Times from the start of drug infusion; all individual values are shown. In addition, mean values for each dose are shown in parantheses. N/A=Not available

	Dose (mg kg^{-1})				
	0.8	1.0	1.2	1.5	1.8
n	1	2	3	2	2
Loss of verbal contact (min)	2.5	(1.00) 1.17,0.83	(1.11) 1.45,1.00, 0.87	(0.91) 0.83,0.98	(0.59) 0.42,0.77
Drop syringe (min)	N/A	(1.17) 1.35, 0.98	(1.01) 1.17,1.25, 0.78	(0.97) 0.95, 0.98	(0 78) 0.78, 0.77
Loss of eyelash reflex (min)	N/A	(2.98) 3.17, 2.80	(2.19) 2.50,1.50, 2.58	(1.45) 1.33, 1.57	(2.27) 0.87, 3.66
Eyes open on command (min)	N/A	(9.96) 5.87, 14.05	(11.72) 17.25,8.78, 9.12	(15.92) 15.50, 16.33	(19.25) 17.5, 21.00
Move limbs on command (min)	N/A	(9.87) 6.23, 13.5	(13.17) 18.00, 10.50, 11.00	(18.14) 16.35, 19.93	(20.00) 19.00, 21.00
Recovery to Ramsay sedation score 2 (min)	N/A	(17.5) 15, 20	(17.33) 20, 20,12	(32.5) 35, 30.	(32.5) 30,35

and was clinically comparable with propofol and thiopentone. After a dose of 1.0 mg kg^{-1}, recovery to eye opening and moving limbs to command took 10 min. Higher doses produced a longer period of unconsciousness. The quality of recovery was good.

Excitatory phenomena were evident in all subjects and appeared to be dose related. Such phenomena ranged from increased muscle tone and shaking, at 0.8 mg kg^{-1}, to prolonged periods of violent coughing and sneezing, at 1.2 and 1.8 mg kg^{-1}, despite apparent anaesthesia. Airway reflexes were considered well preserved and apnoea was not observed.

ELECTROENCEPHALOGRAM

The EEG data were contaminated by large amounts of artefact caused by patient movement in response to questioning by the investigators and by excitatory movements so that it could only be evaluated crudely. The subject receiving the 0.8-mg kg^{-1} dose showed only increased alpha rhythm in association with sedation. Other subjects showed changes typical of anaesthesia with increased delta activity and a reduction in median EEG frequency to 2–3 Hz. No spikes, sharp waves or signs of cortical seizure activity were observed, however, the limited digitization rate and frequency response of the Transmed TM20 system implied that these phenomena may have been undetected.

PHYSIOLOGICAL MEASUREMENTS

During and immediately after infusion of drug, measurement of arterial pressure was compromised by the need for frequent blood sampling; this data set is therefore incomplete. Arterial pressure declined slightly with induction of anaesthesia (median decrease in systolic pressure was 13% at 4 min, largest individual decrease was 22% at 3 min). Heart rate increased immediately after the drug or inactive vehicle was infused (median increase 32% at 1 min, largest individual increase 58% at 1 min); this increase coincided with subjects experiencing pain during injection of inactive vehicle or drug. After loss of consciousness heart rate returned rapidly towards baseline levels but remained slightly elevated (median increase in heart rate 13% between 2 and 10 min). Changes in cardiac output were minimal. Two subjects required assistance to clear an obstructed airway. Apnoea did not occur and ventilation was judged adequate in all subjects. There were no significant biochemical or haematological abnormalities.

PHARMACOKINETICS

When subjects were modelled individually, three compartments (in contrast with two compartments) were justified, both visually and statistically in all cases. A typical subject is shown in figure 2. The model determined from the process of population model building was a three-compartment (non-weight-related) model with log normal inter-individual variation in clearance (*Cl*) and inter-compartmental clearance ($\dot{Q}$). A plot of all C_P values from all subjects against the value predicted by the typical population pharmacokinetic variables confirmed a lack of bias in the population model (fig. 3). Predictions were marginally improved when they were based on individual's pharmacokinetic variables calculated *post hoc*. The variability associated with the η series was quite small and consequently there was little difference between the prediction based on typical population values or individual values for pharmacokinetic variables (fig. 3) These *post hoc* η

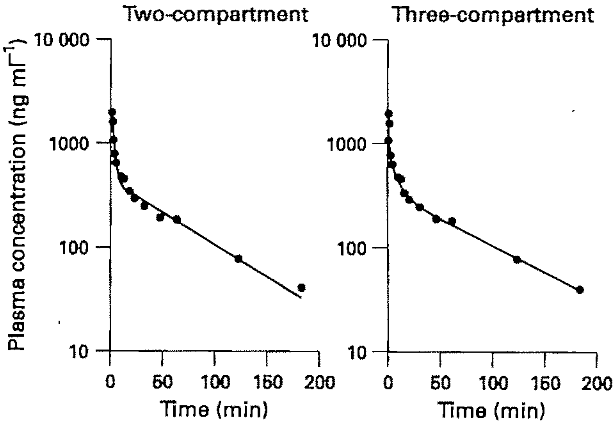

Figure 2 An example of data from a single subject fitted to two- and three-compartment models. Visually and statistically the three-compartment model is prefered.

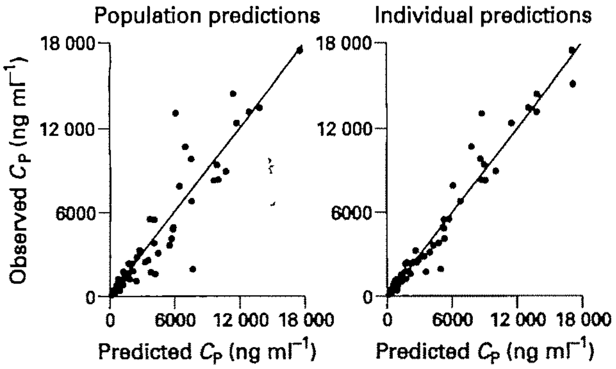

Figure 3 Predicted plasma concentrations (C_P) plotted against observed plasma concentrations based on typical population values and individual values.

Table 2 Typical population values (with variability) for the pharmacokinetic variables describing the time course of concentration of ORG 21465. *95% CI is a measure of the precision of the typical value. The true typical value has a 95% chance of falling within these limits. **CV is the residual unexplained variability; 95% of values will fall inside the typical value plus twice this value and the typical value minus twice this value. With NONMEM the variability is encoded into the structure of the model and if no value is present then there are insufficient data to fit such a variable and the variability cannot be determined

	Typical value	95% CI*	CV**
Clearance (litre min^{-1})	1.55	1.45–1.65	12%
$\dot{Q}_1$ (litre min^{-1})	2.54	1.41–3.66	42%
$\dot{Q}_2$ (litre min^{-1})	1.79	1.07–2.51	42%
V_1 (litre)	4.31	3.84–4.77	
V_2 (litre)	14.2	1.31–1.52	
V_3 (litre)	89.4	78.2–101	

values (the value by which the typical population pharmacokinetic variable must be adjusted to give an individual's value) were plotted against weight to confirm that there was no justification to model pharmacokinetic variables on a weight basis. There was no indication that the pharmacokinetic variables should be modelled as functions of weight; indeed when attempts were made to model with variables related to weight the overall prediction based on population PK typical values was clearly erroneous and the predicted *vs* observed values plot demonstrated systematic misfit. The values and variability of the variables determined for this model are shown in table 2.

Discussion

An ideal i.v. anaesthetic would provide smooth induction of anaesthesia, haemodynamic stability and rapid recovery without accumulation after prolonged administration. It would also be water soluble, free from histamine release or adrenocortical suppression, and unsupportive of bacterial growth. A high therapeutic index would be advantageous. The current i.v. anaesthetic agents propofol, thiopentone and etomidate offer these characteristics to varying degrees, although none is water soluble. Anaesthetic steroids have modest haemodynamic effects and are removed rapidly from the body by hepatic metabolism and elimination; they also have high therapeutic indices.[14] It is these characteristics which have encouraged further development of anaesthetic steroids. Preclinical evaluation of ORG 21465 suggested that it had the characteristics of an excellent i.v. anaesthetic[15] and its progress from laboratory studies to humans was logical.

Although we injected ORG 21465 as an aqueous solution, all subjects reported pain on injection of both the inactive vehicle (water and buffers) and ORG 21465 itself, suggesting that the formulation may need adjustment.

We have confirmed that ORG 21465 is an anaesthetic for humans with onset of anaesthesia within 45–60 s of the start of injection according to dose and choice of end-point for induction. Similar induction times are seen with other agents. Assessment of induction times in this study was complicated by the different rates of drug administration to our individual subjects; studies with other agents have demonstrated that induction times of i.v. anaesthetic agents are dependent on the rate at which they are infused.[11 18] All subjects received the drug over 1 min; this fixed period was chosen to facilitate pharmacokinetic analysis while being clinically realistic. In all animal studies of ORG 21465 the drug was injected over 10 s.[15]

Our investigation was not a formal dose-finding study, however, our data suggest that when ORG 21465 is infused into humans over 1 min, the induction dose is approximately 1 mg kg^{-1}. Recovery from anaesthesia was slower than might be expected with induction doses of thiopentone or propofol, with some subjects requiring 35 min to return to a Ramsay score of 2.

The haemodynamic data collected in this study were limited by frequent sampling of arterial blood. We did not observe gross changes in arterial pressure but it would be premature to assume that anaesthesia with ORG 21465 is haemodynamically stable.

The main side effect of ORG 21465 was excitation with movements, which affected all parts of the body. A wide range of excitatory effects have been associated with i.v. anaesthetic agents, most notably with etomidate and methohexitone but also with propofol, eltanolone, midazolam and thiopentone.[6 19] Our EEG data were limited and this reflects the basic apparatus and need to intermittently stimulate the subjects to assess hypnosis. More accurate EEG recording requires more electrodes, better equipment and an unstimulated subject; reliable detection of spikes and sharp waves in the EEG requires a high digitization rate. Nevertheless, we saw no evidence of cortical excitation. Although technical limitations imply that some spikes might have been undetected by our apparatus, it is probable that the excitation caused by ORG 21465 is of sub-cortical origin. This can only be confirmed by additional studies with more advanced EEG recording.

We have demonstrated that ORG 21465 was an effective i.v. anaesthetic in humans and shared some of the properties of other anaesthetic steroids. It would therefore seem an agent worth further study. Particular attention should be paid to its EEG effects and recovery characteristics.

Acknowledgements

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Computer-controlled infusion of ORG 21465, a water soluble steroid i.v. anaesthetic agent, into human volunteers

J. R. Sneyd, P. M. C. Wright, D. Harris, P. A. Taylor, P. C. M. Vijn, M. Cross,
H. Dale, G. Voortman and P. Boen

Summary

ORG 21465 has been found to possess anaesthetic properties in humans and its pharmacokinetics are known. We performed this study to confirm the characteristics associated with its administration and to define its pharmacodynamic profile, in particular to explore the relationship between sedation, anaesthesia, excitation and plasma drug concentrations. A water soluble preparation of ORG 21465 was administered to six male volunteers as a series of three 15-min computer-controlled, pharmacokinetic model-driven infusions targeting three exponentially increasing plasma concentrations: 0.5, 1 and 2 $\mu g\ ml^{-1}$. The clinical characteristics of the resultant sedation and anaesthesia were observed. Plasma concentrations of ORG 21465 were measured during and for 500 min after the infusions and the EEG recorded. A sigmoid e-max effect compartment pharmacodynamic model was fitted to the plasma concentrations and an EEG derivative (spectral edge frequency (SEF)). Anaesthesia with ORG 21465 was associated with involuntary movements in all subjects. A steady state concentration of 1180 ng ml^{-1} depressed SEF by 50%, the Hill factor describing the sigmoid nature of the concentration–response curve was 1.42 and the equilibration rate constant of the biophase was 0.112 min^{-1}. Anaesthesia with ORG 21465 was found to be unsatisfactory because of involuntary movements and slow equilibration with the biophase. (*Br. J. Anaesth.* 1997; **79**: 433–439).

Key words
Anaesthetics i.v., steroid. Pharmacology, ORG 21465. Sedation. Pharmacodynamics.

ORG 21465 is a water soluble preparation of (2β, 3α, 5α)-3-hydroxy-2-(2,2 dimethylmorpholin 4-yl) pregnane-11,20-dione. In preclinical testing in mice, rats, dogs and monkeys, ORG 21465 appeared safe and potentially suitable as an i.v. anaesthetic in humans.[1] Infusion into 10 human volunteers of ORG 21465 0.8–1.8 mg kg^{-1} over 1 min induced sedation or anaesthesia without histamine release. Excitatory phenomena were observed in all subjects and were dose related; no spikes were seen on the EEG.[2] This previous study also established the pharmacokinetics of ORG 21465 in humans.

We report an open study evaluating the pharmacodynamics of ORG 21465. A computer-controlled drug infusion was used to maximize the experimental return from a small number of subjects. Spectral edge frequency was used to quantify the CNS effect of the agent.

Subjects and methods

SCREENING AND PREPARATION OF SUBJECTS

Six healthy male volunteers who had previously received a bolus of ORG 21465 returned for a second administration. The screening procedure is described in our accompanying article.[2] All subjects gave informed written consent and the study was approved by the local Ethics Committee. Consecutive subjects were studied at intervals of at least 24 h, allowing time to evaluate analysis of follow-up blood samples obtained 24 h after administration of the dose from the previous subject but one.

Subjects were admitted to hospital the night before drug administration and underwent a physical examination and urine screening for drug abuse or alcohol (Merck Triage kit). Subjects were fasted from 22:00 and permitted to drink water until midnight. At 06:00 Hartmann's solution was infused at a rate of 3 ml kg^{-1} h^{-1} into the non-dominant forearm. One hour before the drug infusion, a cannula was placed in the non-dominant radial artery and a long venous catheter (Abbot Ireland Ltd) was advanced from the antecubital fossa of the

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J. R. Sneyd, MD, FRCA, P. M. C Wright*, MD, FFARCSI, D Harris, FRCA, P. A. Taylor, FRCA, P C. M. Vijn†, PHD, M. Cross‡, MB, BCHIR, H. Dale‡, RGN, G Voortman†, P Boen§, MD, Department of Anaesthesia, Derriford Road, Derriford Hospital, Plymouth PL6 8DH UK. Accepted for publication: June 3, 1997.

*Academic Department of Anaesthesia, University of Newcastle, Newcastle.

†NV Organon, Oss, The Netherlands.

‡Phase I Trials Unit Ltd, The Old Convent of Notre Dame, 119 Looseleigh Lane, Derriford, Plymouth PL6 5HH.

§Organon Teknika N V, Turnhout, Belgium.

Correspondence to J. R. S.

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dominant forearm into the thorax to provide central venous access for drug administration. Oxygen was administered by a single nasal cannula and a capnograph sampled airway gas from the contralateral nostril.

DRUG ADMINISTRATION

ORG 21465 was formulated in a buffered aqueous solution at a concentration of 10 mg ml^{-1}. After preparation subjects rested for a minimum of 20 min before administration of ORG 21465 which commenced close to 10:00. Each subject received ORG 21465 as a computer-controlled infusion over 45 min, aiming to achieve stable arterial plasma concentrations of 0.5, 1 and 2 mg ml^{-1} for three consecutive periods of 15 min. This was administered from a Harvard 22 electronic syringe pump controlled by an Elonex 386 personal computer running the pharmacokinetic modelling and drug infusion software STANPUMP (version June 13, 1995).(STANPUMP is freely available from the author, Steven L. Shafer, MD, Anesthesiology Service (112A) PAVAMC, 3801 Miranda Avenue, Palo Alto, CA 94304, USA and on the World Wide Web at http://pkpd.icon.palo-alto.va.gov.) The three-compartment pharmacokinetic model used to control the pump was determined during interim modelling (developed in the course of the previous study which included these six volunteers) and made the assumption that the variables of the model would be related to weight. It had the following variables: V_1 0.246 litre kg^{-1}, k_{10} 0.074667 min^{-1}, k_{12} 0.062 min^{-1}, k_{13} 0.27333 min^{-1}, k_{21} 0.0056167 min^{-1} and k_{31} 0.077167 min^{-1}, where V_1=central volume of distribution and k_{xy} are inter-compartmental rate constants.

The drug delivery system was tested to confirm performance using an Ultramedic SDA 1 computerized syringe tester (Ultramedic Ltd, Wavertree, Liverpool L13 1EJ). Dynamic performance of the entire system was tested over two complete runs of the three-step infusion. Actual performance of the drug infusion system during the clinical study was confirmed by weighing.

MEASUREMENTS

Clinical observations and measurement of physiological variables mirrored the previous study and have been described in detail elsewhere.[2] Briefly, the behaviour of the subjects was recorded using video cameras, arterial pressure was monitored invasively and cardiac output non-invasively. Times to cessation of speech, eye closure, loss of eyelash reflex and return of eye opening and limb movement to command, and recovery to a Ramsay sedation score[3] of 2 were recorded. Excitation was quantified by a single observer who reviewed all video tapes in a single 2-day period. Using a custom-written computer program synchronized with the video timing signals, every individual excitatory movement was identified and graded on an arbitrary 10-point scale where minor movements only visible on close-up (e.g. tremor of a digit or slight facial twitching) scored between 1 and 3; larger movements ranging from myoclonus to major spasms of the whole body scored between 4 and 10. A movement score was calculated for epochs of 1 min duration by summing the excitation scores of each excitatory event during that particular epoch. Thus five myoclonic jerks each scored as 6 on the arbitrary scale would give a movement score for that minute of 30.

Blood sampling and assay for ORG 21465

Venous blood was obtained before the study and at 24 and 72 h for measurement of a wide range of biochemical and haematological variables.

Arterial blood samples were obtained immediately before drug administration, at 5-min intervals during infusion and at 5, 10, 15, 20, 25, 30, 40 and 50 min and 1, 1.25, 1.5, 1.75, 2, 2.25, 2,75, 3, 3.5, 4, 4.5, 5, 6, 7, 8, 9 and 10 h after infusion. The 15-, 30- and 45-min samples during infusion of the drug were obtained immediately before the change of infusion rate. Samples (5 ml) were transferred to heparinized tubes, cooled and centrifuged within 1 h at 3000 rpm for 10 min. The separated serum was subsequently stored at −20 °C until analysis.

Concentrations of ORG 21465 in serum were measured with a capillary gas chromatographic assay with mass-selective detection (GC-MS) after n-hexane extraction. Details of the analytical method and its accuracy have been reported in our previous study.[2]

Electroencephalogram (EEG) recording

The EEG was recorded from seven positions overlying cortical motor and sensory areas. Electrodes were silver–silver chloride cups filled with conducting paste and mounted with collodion. Expressed in 10-20 system co-ordinates, which is the standard in EEG montage, the positions were at F3, Fz, F4, C3, C4, P3 and P4. A common reference electrode was used at position Cz. All electrode impedances were less than 5 kΩ. The wires from the electrodes to the pre-amplifiers were short and shielded for optimal signal-to-noise ratio. The pre-amplifiers were fitted in a small battery powered unit connected to the main amplifier unit by an optical link.[4] The amplified analogue signals were filtered (0.3–200 Hz), digitized at 1000 Hz with 12 bits (1:4096) precision and stored on opto-magnetic computer media. Synchrony between the TCI system and the EEG recorder was maintained by time markers stored with the EEG signals.

Analogue data were also led to a video processor that constructs constantly scrolling EEG traces on the left half of a video screen together with the images of one of the cameras on the right half of the screen. The combined images of EEG traces and camera were stored on VHS video tape.

The EEG was inspected visually for artefacts. Eye blinks give rise to characteristic, moderate amplitude waveforms in the EEG, facial and neck muscle activity gives high frequency components and gross movements give baseline shifts with very low frequencies. After visual inspection of all EEG data as consecutive 5-s epochs, artefacts were marked and excluded automatically from further analysis. Spectral edge frequency (SEF) was calculated as follows: each accepted epoch was transformed to a power spectral density curve by Fourier transformation followed by power conversion (the modulus of the square of the complex values). For each spectrum the power present in the frequency band of 0.6–48 Hz was calculated and normalized to 100%. SEF was determined such that the power present in the band between 0.6 Hz and this SEF was equal to 95%.

Electromyogram (EMG) recording

In the final subject two electrodes were placed 6 cm apart in the pectoralis major at a position where previous subjects showed pronounced muscle activity. The differential signal was band-filtered (100–300 Hz) and the envelope (rectification, followed by low pass filtering) of this signal was stored as an additional channel with the EEG. The onset of EMG bursts were marked with time markers and 1-s segments of the EEG centred on the marker were extracted. All selected segments were averaged.

PHARMACOKINETIC AND PHARMACODYNAMIC ANALYSIS

Our accompanying article describes the estimation of the pharmacokinetic parameters of ORG 21465.[2] The purpose of the studies presented here was to estimate the parameters of a pharmacodynamic model. To achieve this our only prerequisite was to describe the observed plasma concentration profile well in each individual; the actual pharmacokinetic model used was unimportant. All modelling was performed using NONMEM Version IV level 2.1 (University of California).[5]

For the purpose of the current analysis a population pharmacokinetic model was fitted to the plasma concentrations obtained during and after the target-controlled infusions (six subjects) and the data from the previous bolus dose study (10 subjects). No attempt was made to build the population model, but rather the structure of the population model determined during the previous analysis was used with one additional parameter. Because the formulation of the drug and its method of administration differed during the infusion compared with the bolus study we allowed the bioavailability to vary between these two administrations. We then obtained Bayesian estimates of each individual's pharmacokinetic variables using the *post hoc* step of NONMEM. This approach permitted us to estimate afresh the pharmacokinetic variables after administration of a larger dose of drug compared with previously and also to describe well the observed plasma concentrations. Each individual's pharmacokinetic parameters were then incorporated into NONMEM's input to enable the development of a population pharmacodynamic model.

A pharmacodynamic model was fitted to the SEF data from each individual. SEF values at 1-min intervals during the target-controlled infusions and for 45 min after drug administration was discontinued were included in the data set. All SEF values were referenced to the value immediately before drug administration which was considered as unity. Effect was modelled to follow a sigmoid relationship to a maximum value of 100% as anaesthetic concentration in a hybrid effect compartment increased. The slope of the concentration–effect relationship was defined by the variable gamma (γ) and the concentration giving 50% reduction in the SEF as C_{50}. The effect compartment was of minimal volume but with its own rate constant (k_{e0}). We also modelled an increase in SEF which multiplied the value that it otherwise would assume (beta activation factor). This effect was modelled as occurring when any anaesthetic was present in the system.

We next built a mixed effects pharmacodynamic model. The mixed effects approach defines a single basic model of typical values (population means) for the pharmacodynamic parameters; variations in each individual from the basic model are defined by the use of a variable number of additional, user-defined "inter-individual variability" parameters each defining a degree of variability in one or more of the basic variables. For example, C_{50} was modelled as:

$$C_{50}=C_{50\text{typical}}\times\exp(\eta)$$

where C_{50}=value for an individual, $C_{50\text{typical}}$=typical value for the population, and η=a normally distributed random variable with mean zero. We added inter-individual variation parameters until no further modelled variation could be justified. The justification for each additional inter-individual variation parameter was for it to improve the goodness of fit statistic (−2 log likelihood) by >3.8 (evaluated against the chi-square distribution this is equivalent to significance at the 0.05 level) and to result in a visual improvement in the goodness of fit.

Results

We studied six male subjects, aged 22–30 yr, weighing 63–82 kg. The performance of the infusion system was satisfactory during bench testing. Measured errors during steady infusion at 10, 100 and 1000 ml h^{-1} were −0.53%, −0.91% and −0.6%, respectively. During dynamic testing over two complete runs of the three-step drug infusion with the pump driven by the STANPUMP software, the greatest measured error was 2.4% at 5 min which decreased progressively to 1.08% at 15 min and to 0.75% at 45 min. Weighing of the infusion syringes used during the study confirmed that the correct volume of drug had been infused.

CHARACTERISTICS OF ANAESTHESIA

None of the subjects reported discomfort during central venous injection of ORG 21465. There were no cutaneous or cardiovascular signs of histamine release. All subjects were sedated at the lowest target concentration infusion (0–15 min, target plasma concentration of 0.5 mg ml^{-1}). Five subjects became anaesthetized during the second stage of the infusion

Table 1 Clinical responses to ORG 21465; all values are time (min) after drug administration

	Subject No.							
	1	2	3	4	5	6	Mean	SD
Time to speech cessation	16.5	31.0	16.6	21.4	15.0	17.0	19.6	5.5
Time to eye closure	16.8	Closed	Closed	Closed	15.0	Closed		
Time to loss of eyelash reflex	17.1	31.0	18.9	22.2	24.0	17.4	21.8	4.8

Table 2 Recovery from anaesthesia with ORG 21465; all values are time (min) after discontinuation of a 45-min infusion

	Subject No.							
	1	2	3	4	5	6	Mean	SD
Eyes open on command	31.0	19.2	10.3	12.7	38.0	14.2	20.9	10.2
Move limbs on command	31.8	N/A	13.2	67 0	28.0	20.0	32.0	18.6
Recover to Ramsay score 2	34	30	40	20	40	30	32.3	6.9

(15–30 min, target plasma concentration of 1 mg ml^{-1}) with loss of verbal contact and loss of eyelash reflex. The remaining subject became anaesthetized during the third stage of the infusion (30–45 min, target plasma concentration of 2 mg ml^{-1}). Times to loss of verbal contact and eyelash reflex were variable (table 1) and recovery from anaesthesia was slow (table 2). No subject moved in response to verbal command within 10 min of the end of drug infusion.

Systolic and diastolic pressures declined slightly with anaesthesia (fig. 1). Heart rate increased progressively between 30 and 45 min which coincided with the peak period of excitation. Some respiratory depression was evident in three subjects, of whom one became apnoeic and required assisted ventilation.

Excitatory phenomena were evident in all subjects and appeared to be dose related. Such phenomena ranged from increased muscle tone and twitching to extreme coughing and sneezing. Typically, excitation commenced with twitching of the fingers and developed into movements of the upper limbs and torso. In most subjects, hypertonia of the lower limbs was noted with extension at the knees, ankles and toes. There was no hyperreflexia and the plantar response remained down-going. In two subjects, a few beats of ankle clonus were elicited at the peak of excitation. Minor stimuli resulted in marked withdrawal of the limb. Excitation occurred before loss of consciousness and continued into the recovery phase; two subjects described feeling twitchy after recovery from anaesthesia. Movement scores were determined for five subjects (fig. 2). In the remaining subject, excitation was mainly coughing and sneezing and appeared qualitatively different from the other five subjects. For this reason no attempt was made to quantify this subject's excitation. All subjects reported favourably on their experiences.

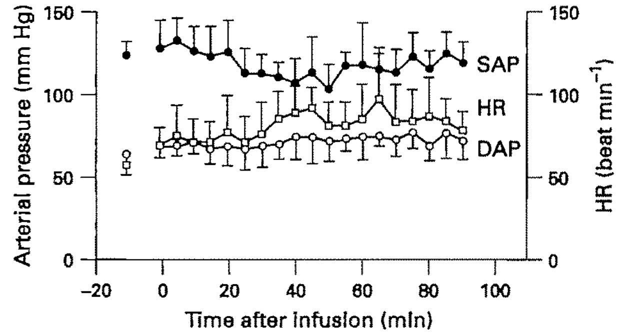

Figure 1 Systolic (SAP) and diastolic (DAP) arterial pressures and heart rate (HR) before, during and after a three-stage 45 min infusion of ORG 21465. Times are from the start of infusion. Baseline measurements recorded before instrumentation and cannulation are shown for comparison.

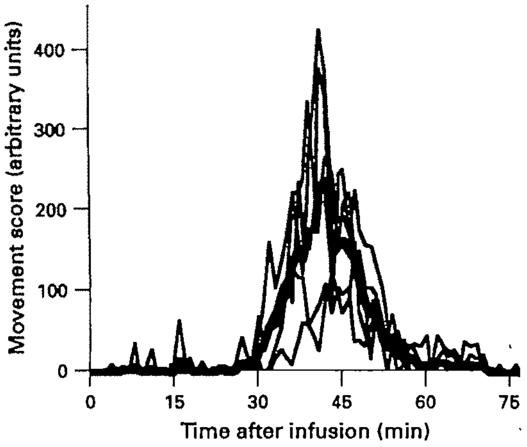

Figure 2 Movement scores for five subjects. All excitatory movements were graded by severity on an arbitrary 10-point scale. The movement score is the sum of individual scores of all movements occurring within a 1-min period. Scores for individual subjects are shown as thin lines; bold line=group average.

EEG

EEG recordings showed changes typical of anaesthesia: a gradual increase in amplitude and shift from desynchronized fast activity towards synchronized slow activity. Except for a few spikes with moderately fast rise times and waves with moderately sharp aspects, no consistent signs of epileptic activity were observed. These sharp waves did not coincide with involuntary movements. During involuntary movements no abnormal patterns were observed in the EEG.

Typical drug effects in the EEG were: theta activity 3 min after the start of infusion, preceded or followed by an increase in alpha activity, then slow delta waves at 4–10 min. Initially, these delta waves were accompanied by faster activity, beta activation, which remained present during the second infusion period and disappeared with the third infusion. The third infusion was associated with increased delta amplitude leading to periods of burst suppression. Recovery after drug withdrawal started with reappearance of high frequency components. Next the delta activity accelerated and was gradually replaced by theta, alpha and occasionally beta activity.

The EEG data were summarized quantitatively in the SEF. Before drug administration, the SEF fluctuated at around 15 Hz with wide individual variation. During the first infusion SEF increased abruptly and reached a maximum value of 25 Hz, thereafter decreasing monotonically and, by the end of the first infusion period, SEF values (typically) approximated pre-drug values. After the start of the second infusion period, the SEF decreased monotonically in all subjects to, typically, 10 Hz. The start of the third infusion caused a further rapid decrease in SEF to, typically, 5 Hz. After the end of drug delivery, SEF values increased immediately and monotonically, reaching pre-drug values at, typically, 90 min.

EMG

In the single subject studied, trains of EMG bursts occurred periodically, with a mean interval of 380 ms between bursts, and a median of 3 bursts per train. A total of 777 bursts in 245 trains were observed. The trains of EMG bursts coincided with visible activity of the muscle on the synchronized video recordings. To avoid confusing a cortical somatosensory response to the bursts with a true cortical origin, only the first EMG burst of each train was included in the averaging procedure. The result of the averaging process of the EEG and the EMG traces triggered by the onset of bursts is shown in figure 3. No significant deflections of the averaged EEG were observed before the start of the first EMG burst of each train.

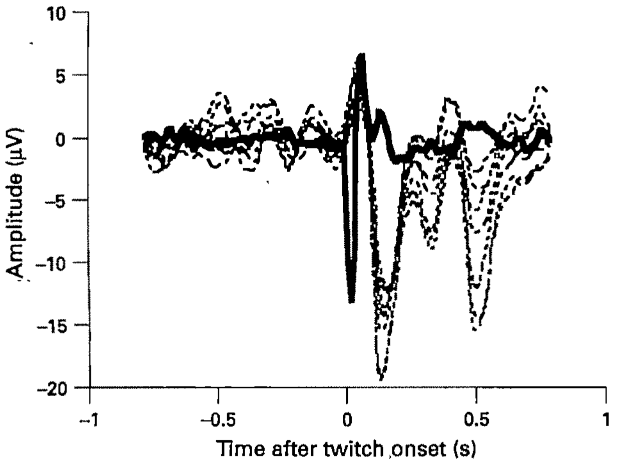

Figure 3 EEG (seven channels; thin lines) and EMG (one channel; bold line) averages triggered on the onsets of the first burst of EMG trains (n=245).

Table 3 Typical population values (with variability) for the pharmacokinetic variables describing the time course of concentration of ORG 21465. Model fitted to data from both the previous bolus dose study and the target-controlled infusion study. *95% CI is a measure of the precision of the typical value. The true typical value has a 95% chance of falling within these limits. **CV is the residual unexplained variability, 95% of values will fall inside the typical value plus twice this value and the typical value minus twice this value. With NONMEM the variability is encoded into the structure of the model and if no value is present then there are insufficient data to fit such a variable and the variability cannot be determined

	Typical value	95% CI*	CV**
Clearance (litres/min^{-1})	1.50	1.30–1.70	10%
$\dot{Q}_1$ (litres/min^{-1})	2.85	1.97–3.73	29%
$\dot{Q}_2$ (litres/min^{-1})	0.603	0.475–0.731	29%
V_1 (litres)	6.39	5.01–7.77	
V_2 (litres)	46.0	35.5–56.5	
V_3 (litres)	123	78.2–168	
Bioavailability (TCI/bolus)	1.34	1.23–1.46	

Table 4 A population pharmacodynamic model with inter-individual variation in C_{50} and in the factor multiplying SEF when anaesthetic is present. No additional inter-individual variation could be determined. **CV is the residual unexplained variability, as presented 95% of values will fall inside the typical value multiplied by this value and the typical value divided by this value. *95% CI is a measure of the precision of the typical value. The true typical value has a 95% chance of falling within these limits. In the case of the beta activation factor variability was coded as SD (not CV) and consequently this value is SD

	Typical value	95% CI*	CV**
k_{e0} (min^{-1})	0.112	0.102–0.121	
C_{50}(depression) (ng ml^{-1})	1180	974–1386	26%
γ	1.42	1.32–1.51	
Beta activation factor	1.44	1.20–1.67	0.32

PHARMACOKINETICS

We used the structure of the pharmacokinetic model determined using data from the bolus study (i.e. a three-compartment (non-weight-related) model with log normal inter-individual variation in clearance (Cl) and inter-compartmental clearance ($\dot{Q}$)). We also allowed bioavailability to vary from the bolus to the infusion encounter because the drug was formulated differently and given by a different route. The variables of this model fitted to data from both bolus (10 subjects) and infusion (six subjects) studies are given in table 3. The model gave a good description of the observed plasma concentrations in all subjects.

A population pharmacodynamic model with inter-individual variation in C_{50} and in the beta activation factor was supported by the data (table 4). No additional inter-individual variation could be determined. In all individuals it fitted well the observed SEF values.

Discussion

The aim of this study was to determine the clinical characteristics of anaesthesia with ORG 21465 in humans. We also wished to elucidate further the time course of anaesthesia and how this time course can be related to the concentration of the drug in plasma. We chose a sophisticated study design with computer-controlled drug infusion and multiple end-points. Drug development is expensive and time consuming and not without risk to the volunteer subjects. Investigators therefore have a responsibility to obtain the most information from each human exposure. Our design allowed us to maximize the information yield while remaining within the dose supported by animal administrations and limiting anaesthesia and recovery time. As expected, ORG 21465 induced anaesthesia in all of our subjects with minimal effects on cardiovascular variables. As before, the drug caused dose-related involuntary movements (excitation) to some degree in all subjects. We were also able to demonstrate that the effect of the drug on the SEF could be modelled assuming a simple sigmoid concentration–response relationship and that the site of action of the drug (biophase) equilibrated slowly with the concentration of drug in plasma.

One of the main purposes of this study was the determination of the pharmacodynamic characteristics. To do this we chose to administer target-controlled infusions at three different target concentrations. This is a departure from the "usual" method used to determine the equilibration rate of a drug with its biophase, that is infusing a drug at a relatively slow rate until almost maximum effect is observed, then discontinuing the drug. During and after this administration, drug concentration and effect are measured and effect is plotted against drug concentration. The rate of equilibration is calculated to explain the hysteresis between the onset and offset curves. We devised our method because we were uncertain how much drug would be required to give nearly maximum effect, and (given the paucity of data for this drug in humans) we were severely constrained in the total quantity of drug that we could give to each volunteer. The method that we used aimed to produce an early constant quantity in plasma and then calculate a rate constant directly from the resultant time course of effect. Using this method we were able to determine exactly how much drug would be given in advance and thereby give the maximum permissible to each volunteer and maximize the quantity of information obtained. We also hoped that the three infusion targets would approach a stable effect on each occasion and would thus give three points on the concentration–effect curve. This design gave us a large amount of information which could be confidently modelled but we are left with some reservations.

To produce an early constant concentration in plasma required that the model used to drive the infusions was correct and predictive. In part because of time constraints, we chose a model with its variables related to weight; this proved not to be a very predictive model. Later we chose a much more predictive pharmacokinetic model; this discrepancy is of no consequence as the doses given were known. However, because the model used to determine dosing was not closely predictive, the plasma concentrations during the target-controlled infusions were not constant, particularly early in each infusion. A second reservation was that SEF continued to change at the end of each infusion target. Thus steady state was not approached and our ability to determine three points on the concentration–effect curve was compromised. However, the iterative modelling process we used to determine the pharmacodynamic model is insensitive to both these limitations and we were not prevented from confidently determining the pharmacodynamic variables.

We included a beta activation factor in the pharmacodynamic model because this improved the model and is intuitively sensible. EEG activation during sedation is well recognized[6] and the spectral edge seldom has a true monotonic relationship with drug concentration unless induction of anaesthesia is very rapid when activation becomes short or even absent. In our subjects, sedation (time to speech cessation) lasted 15–31 min and EEG activation was obvious.

We found that ORG 21465 equilibrated slowly with the biophase with a k_{eo} value of 0.112 min^{-1}. The time required for the biophase concentration to reach 50% of the plasma concentration ($T_{1/2}\ k_{eo}$) can be calculated as $0.693/T_{1/2}\ k_{eo}$ which for ORG 21465 is 6.19 min. This is comparable with that reported for eltanolone (6.9 min)[7] but much slower than thiopentone (0.58 min).[8] Anaesthetists value drugs which "act quickly" and biophase equilibration is an important determinant of onset (and offset) of drug action. For a new i.v. anaesthetic to be successful, whether water soluble or not, it would need rapid biophase equilibration. This factor may in part explain the failure of eltanolone and gives a clear target for other candidate i.v. agents. The physicochemical determinants of $T_{1/2}\ k_{eo}$ are currently unclear. Water solubility alone cannot be the only factor as the water soluble opioids alfentanil and remifentanil equilibrate rapidly ($T_{1/2}\ k_{eo}$ 0.96 and 1.6 min, respectively).[9]

The degree of excitation observed during this study was greater than that seen with any currently used i.v. anaesthetic agent, including methohexitone and etomidate. The excitation seen was clinically unacceptable and its appearance during light sedation with persistence through light and deep anaesthesia into recovery eliminates any possibility that it might be avoided by judicious dosing or restricting the agent to sedation. Our attempt to quantify excitation using an arbitrary 10-point scale has its limitations; nevertheless, the use of a single assessor reviewing all the videotapes consecutively made the process as objective as possible. It is clear from figure 2 that excitation was greatest at higher plasma concentrations of ORG 21465. The scale of excitation ranged from minimal to severe and it is of interest that subjects who experienced the most excitation during the bolus study were also the most affected during the infusion study. These clinical characteristics are similar to anaesthesia with other steroids[10] and will certainly prevent the use of this drug as an anaesthetic in humans. The relationship between the EEG and this excitation deserves some exploration. The EEG contained components that were cortical in nature and related to involuntary movements. Inspection shows that these cortical components followed (rather than preceded) both movement and EMG changes in temporal sequence. This strongly supports the hypothesis that cortical activity is not involved in generating this muscle activity. Because of the lack of cortical activity the involuntary movements are best described as extrapyramidal.

There appeared to be three major problems with ORG 21465. First, pain on injection, which we observed during our previous study (using an aqueous solution of pH 4 administered into a peripheral vein). Pain on injection was not observed during this study because of central venous administration. This permitted the study of a sedative dose of ORG 21465 without modification of its effects by pain. Central venous administration is not a routine route for induction of anaesthesia and were the drug to be developed further, alternative formulations might be investigated. A second major problem was excitation of a degree that is not clinically acceptable to practising anaesthetists and which appeared in all subjects. The final problem was slow equilibration of the drug with the biophase which results in slow induction of anaesthesia, difficulty in titrating dose to effect and slow recovery.

We have demonstrated that this steroidal anaesthetic can induce and maintain anaesthesia with modest haemodynamic changes similar to those seen with other anaesthetic steroids. However, ORG 21465 is not a useful anaesthetic agent for humans.

Acknowledgements

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Prognosis of intraoperative brachial plexus injury: a review of 22 cases

B. BEN-DAVID AND S. STAHL

Summary

A retrospective review over 6 yr of patients presenting to the hand clinic was performed to identify cases of postoperative brachial plexopathy (PBP) and to assess both prognosis and early indices of prognosis. Over this period (1989–1995), 22 patients were referred by the hospital's surgical departments to the hand clinic because of PBP. Eight cases followed open heart surgery (OHS) and 14 followed non-cardiac surgery (NCS). Median full recovery took 10 (range 4–16) weeks and 20 (8–50) weeks, respectively. Long-term follow-up revealed one OHS patient with residual tingling and three NCS patients with residual weakness. Brachial plexopathy after median sternotomy was characterized by a predominance of sensory complaint in the lower roots of the plexus. Injury after non-cardiac surgery was reflected by a predominance of motor deficit in the upper and middle roots. Brachial plexus injury after cardiac surgery carries an excellent prognosis for full functional recovery. Although the limited number of cases precludes statistical substantiation, the data suggest that the prognosis of PBP after non-cardiac surgery may be worse in males, diabetics, those with injury to all roots of the plexus and, when in addition to the motor deficit there is sensory loss and pain or dysaesthesia. At a 1 week "prognostic milestone", 79% of NCS patients with significant symptomatology enjoyed complete recovery although this took as long as 5 months to 1 yr in 50% of patients. At a 6–8 week "prognostic milestone", 50% of those who had not yet had improvement in the motor deficit suffered residual neurological deficit. All patients recovered to a significant extent even when recovery was not complete and none suffered from late deterioration or chronic pain. (*Br. J. Anaesth.* 1997; **79**: 440–445).

Key words
Complications, brachial plexus injury. Nerve, damage (postoperative).

Postoperative brachial plexopathy (PBP) has been documented in the literature for more than 100 yr. PBP is generally believed to be a result of traction injury of the nerves with compression a contributing factor.[1] Both stretching and compression of the nerve ultimately lead to ischaemia of the vasa nervorum and subsequent injury to the nerve.[2–4] In addition, there may be rupture of intraneural capillaries and haematoma formation with further compression.[1] Several factors have been associated with intraoperative brachial plexus injury, including concomitant patient disease, anatomical variations, positioning of the patient, surgical factors and physiological factors (table 1).

The prevalence of PBP has been estimated at 0.02–0.06%.[1,5,6] A recent review of 1541 closed anaesthesia malpractice claims included 227 (15%) for nerve injury. Of these, brachial plexus injury represented 23% and was second only to ulnar neuropathy (34%) in frequency.[7] Insofar as these cases draw from insurance claim files, they almost certainly represent cases of residual loss and dysfunction. Yet previous authors have suggested that the long-term outcome in cases of intraoperative brachial plexus injury is almost invariably good—an apparent contradiction.[1,8–10] Review of the literature regarding prognosis and outcome of PBP reveals a relatively sparse published data base.[1,6,10,11] This is particularly true if one considers separately those cases occurring after non-cardiac surgery.

It is reasonable to assume that an awareness of the potential for brachial plexus and other nerve injuries together with a knowledge of the pertinent anatomy, pathogenesis and associated risk factors should reduce the incidence of these injuries. However, this information is of little practical value when confronted with such a patient after operation. Foremost among the patient's anxious questions will be with regard to prognosis. This retrospective review was undertaken in order to specifically address the question of prognosis of PBP.

Patients and methods

The records of the Rambam Medical Center Hand Clinic were searched for all cases of intraoperative brachial plexus injury occurring during the period 1989–1995. Both clinic and inpatient hospital charts were reviewed thoroughly and the patients, where possible, were contacted for long-term follow-up.

All patients included in this review were those who presented after operation to the hand clinic following surgery at this institution. The data do not include

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BRUCE BEN-DAVID, MD, Department of Anesthesia, Herzliya-Haifa (Horev) Medical Center, 15 Horev Street, Haifa, Israel. SHALOM STAHL, MD, Hand Unit, Rambam Medical Center, Haifa, Israel. Accepted for publication: May 8, 1997.

Correspondence to B. B.-D.

Table 1 Factors associated with intraoperative brachial plexus injury

- Concomitant disease
  - Diabetes mellitus
  - Hypothyroidsim
  - Pernicious anaemia
  - Alcoholism
  - Pre-existing neuropathy
  - Herpes zoster
  - Polyarteritis nodosa
  - Peripheral vascular disease
  - Coagulopathy
- Concomitant anatomical predisposition
  - Cervical rib
  - Scalene muscle hypertrophy
  - Deformity (e.g. post-traumatic) of shoulder region
  - Anomalous derivation of plexus
- Positioning
  - Steep Trendelenburg
  - Steep Trendelenburg+shoulder braces
  - Steep Trendelenburg+wrist suspension
  - Excessive abduction of arm (>90°)
  - Dorsal extension at shoulder
  - Posterior shoulder displacement
  - External rotation of arm
  - Excessive rotation of head
- Surgical
  - Prolonged operative time
  - Median sternotomy
- Physiological
  - Hypothermia
  - Hypotension

those patients who had in-hospital consultations unless the patient went on to receive care through the outpatient hand clinic. No patient presented to the clinic sooner than 1 week after operation. Patients were seen at monthly intervals for 2–3 months after achieving maximum recovery. Long-term follow-up to verify residual injuries and to eliminate the possibility of late deterioration was provided by phone contact during the gathering of data for this review.

Evaluation of all patients included a detailed history covering concomitant diseases and predisposing factors, a clinical history regarding upper extremity pain, paraesthesia, numbness and weakness, and physical examination of all motor and sensory functions supplied by the brachial plexus. Each patient's injury was described by a specific description of the involved nerve roots and by a description of the initial presentation in terms of pain, motor and sensory impairment. For the purposes of this review these disturbances were classified on three-point scales. These scales were: motor: 1=paralysis, 2=paresis, 3=no weakness; sensory: 1=anaesthesia, 2=hypoaesthesia, 3=normal sensation; and pain: 1=frank pain, 2=dysaesthesia, 3=no pain. Electromyography (EMG) was not performed in the early postoperative period as this would only be indicated to validate suspicion of a pre-existing neurological condition.[12] Electrophysiological studies were performed 6–8 weeks after operation, but only in those patients who had yet to demonstrate significant clinical improvement. The purpose of the study was to establish nerve continuity and to serve as a baseline for further evaluation and decision making regarding other intervention (e.g. surgical neurolysis).

All patients were treated in a similar manner. To prevent contractures, occupational therapy was undertaken for splinting of the wrist and fingers where indicated. Weakness resulting in shoulder subluxation or difficulty in elbow flexion was treated with a supportive sling. Active and passive physical therapy was conducted agressively in all patients. Particular attention was paid to full passive range of motion exercises several times a day to maintain joint motion and prevent contractures.

Results

A total of 22 cases of PBP were identified; 14 of these had undergone non-cardiac surgery (NCS) (table 2) and eight had undergone open heart surgery (OHS) with median sternotomy (table 3). In the NCS group there were six women and eight men, with mean ages of 52 and 57 yr, respectively. In the OHS group there were seven males (mean age 62 yr) and one female (aged 45 yr). Both groups had patients with possible contributing factors. Hospital inpatient chart reviews revealed that all patients had undergone general anaesthesia, but none of the charts contained information on the specifics of

Table 2 Cases of postoperative bracial plexopathy following open heart surgery. Initial presentation: motor, 1=paralysis, 2=paresis, 3=no weakness; sensory, 1=anaesthesia, 2=hypoaesthesia, 3=normal sensation; pain, 1=frank pain 2=dysaesthesia, 3=no pain. CABG=coronary artery bypass grafts, MVR=mitral valve replacement

Patient No.	Sex	Age (yr)	Onset of Sx postop.	Presented to clinic (weeks)	Surgery	Possible contributory pre-existing condition	Initial presentation			Injury to roots	Not improved at 6–8 wks	Time to max. recovery (weeks)	Degree of recovery
							Motor	Sensory	Pain				
1	M	61	1 day	5	CABG		2	2	3	C8–T1		13 wks	Full
4	M	50	Immediate	2	CABG		3	3	2	C8–T1		4 wks	Full
7	M	60	2 days	2	CABG		2	2	3	C8–T1		8 wks	Full
14	M	58	1 day	2	CABG	Ulnar cubital syndrome	2	2	1	C8–T1		10 wks	Full
16	F	45	1 day	2	MVR	Cervical rib	3	1	2	C7–T1		16 wks	Full
17	M	58	Immediate	1.5	CABG	History of brachial plexus injury	2	1	1	C7–T1		10 wks	Full
20	M	72	1 day	4	CABG		3	2	3	C8–T1		7 wks	Full
21	M	76	1 day	2	CABG	Diabetes	3	2	2	C8–T1		40 wks	Residual tingling

Table 3 Cases of postoperative brachial plexopathy following non-cardiac surgery. Initial presentation: motor, 1=paralysis, 2=paresis, 3=no weakness; sensory, 1=anaesthesia, 2=hypoaesthesia, 3=normal sensation; pain, 1=frank pain 2=dysaesthesia, 3=no pain

Patient No.	Sex	Age (yr)	Onset of Sx postop.	Presented to clinic (weeks)	Surgery	Possible contributory pre-existing condition	Initial presentation			Injury to roots	Not improved at 6–8 wks	Time to max. recovery (weeks)	Degree of recovery
							Motor	Sensory	Pain				
2	F	55	1 day	3	Hysterectomy	Diabetes	2	2	3	C6–8		16	Full
3	M	62	1 day	3	Aorto-bifemoral	Alcoholism	2	2	1	C5–T1	+	50	Full
5	F	48	1 day	2	Cholecystectomy	Carpal tunnel	2	3	3	C5–6		8	Full
6	M	64	Immediate	2	Abd.-perineal resection		2	3	3	C5–7		15	Full
8	F	70	Immediate	1	Sigmoidectomy		2	2	2	C5–7		29	Full
9	M	72	1 day	1	Aorto-bifemoral	Heavy smoke rperiph. vasc. disease	2	3	3	C5–8	+	20	Full
10	F	32	3 days	1	Road trauma laparotomy, splenectomy		2	3	3	C5–6		16	Full
11	M	70	1 day	3	Hemicolectomy		2	2	1	C5–T1	+	56	Residual weakness
12	M	46	1 day	2	Pancreas transplant	Diabetes	2	2	2	C5–7	+	56	Residual motor and sensory loss
13	F	55	Immediate	1	Shoulder replacement		1	3	3	C5–8		24	Full
15	M	48	1 day	4	Nephrectomy		2	3	3	C5–T1		48	Full
18	M	55	2 days	1.5	Hemicolectomy	Thoracic outlet syndrome	2	2	3	C7–T1	+	26	Full (scalenectomy at 18 weeks)
19	M	38	1 day	3	Road trauma pinning femur, tibia fxs, laparotomy		2	2	2	C5–8	+	32	Residual weakness
22	F	54	2 days	3	Hysterectomy	Carpal tunnel	2	3	3	C5–7		10	Full

intraoperative positioning or arm positioning. None of the patients had undergone regional anaesthesia of the neck or upper extremity. All operations were of more than 2 h duration but there was no correlation between duration and long-term outcome. Because of the retrospective nature of the study and the limited method of case collection, no attempt was made to estimate incidence data from the total number of surgical cases over this period.

In the OHS group, seven of eight patients achieved full recovery over a median of 10 (range 4–16) weeks. One patient, a diabetic, suffered from a persistent tingling sensation in the affected hand. All had suffered injury to the roots of the lower trunk (C8, T1) with two also having injury to the middle trunk (C7). In the NCS group, three of 14 patients failed to achieve full recovery although all patients improved substantially. Injuries included roots of upper and middle trunks in all but one patient (No. 18). Three patients (Nos 3, 11 and 15) had injury inclusive of all roots of the plexus. For patients who recovered fully, the median time to recovery was 20 (range 8–50) weeks after operation. Six patients had no evidence of motor improvement by 6–8 weeks after operation and were studied by EMG. This continued evaluation, and a prior history of thoracic outlet syndrome, led to scalenectomy in patient No. 18, the result of which was complete neurological recovery. Age had no apparent influence on the likelihood of residual injury. All four patients with residual injury were male. While suggestive of an influence of gender on outcome (non-significant by Fisher's exact test) the small number of patients precluded meaningful statistical analysis. The same was true for the influence of "predisposing factors"; nine of 22 patients had some predisposing factor (see table 1) and two had a history of prior carpal tunnel release. It is uncertain if this is any different from the incidence of such factors in the general population of surgical patients. Of the four patients with residual injury, two had no predisposing factors and two were diabetic. That two of three diabetics with PBP had residual injury may suggest a poorer prognosis among diabetics.

The clinical presentation differed between OHS and NCS groups. In the former, sensory impairment and pain–dysaesthesia were the prominent and consistent features. No patient had isolated or predominant motor loss and six of eight patients had sensory–pain disturbance without motor loss or of greater degree than the motor loss. In the NCS group the opposite was true. Here, motor deficit was the prominent and consistent feature. There appears to be no indication of prognosis in the particular degree and features of the initial presentation. The one exception to this was for NCS-PBP where patients with pain–dysaesthesia tended to have a prolonged recovery. Further, all three patients with residual injury had pain–dysaesthesia. Also, patients with injury to all roots tended to have incomplete or prolonged recovery.

Six NCS-PBP patients had no motor recovery by 6–8 weeks. This group included all three patients with residual injury; that is 50% of patients with no motor recovery by 6–8 weeks ultimately had a residual deficit. There were several other observations related to recovery; motor recovery proceeded in a caudad–cepahalad direction with the lower roots recovering sooner. Sensory recovery appears to precede motor recovery and failure to observe any sensory recovery by 3–4 weeks may also be an ominous prognostic milestone. *All* patients exhibited significant recovery even if recovery was not complete; temporal progression was always in the direction of recovery with no patient exhibiting deterioration. No patient in this series suffered chronic pain.

Discussion

The most striking finding of this study was the disparate outcomes for the OHS compared with the NCS group. Although there was no significant difference in the quantitative incidences of residual injury (one of eight patients compared with three of 14 patients) there was a *qualitative* difference. In the OHS group, one of eight patients suffered a mild residual tingling sensation whereas in the NCS group, three of 14 suffered residual weakness. These values are in contrast with existing opinion that nearly all intraoperative brachial plexus injuries recover, and perhaps explains the prevalence of this complication in the insurance industry data.

It must be acknowledged that our methodology of case collection skewed the prognostic significance of these data to the pessimistic. A retrospective review of only those cases presenting to the hand clinic more than 1 week after operation eliminates those cases of mild and transient injury and may preferentially select those cases of motor complaint over those with sensory complaint. It has been reported that most cases of PBP after sternotomy are already asymptomatic at the time of hospital discharge.[13] Parks[6] reported 25 cases of PBP of whom eight suffered mild injury and recovered in an average time of 9 days. Of the remaining 17 patients, 14 recovered within 6 months and three had residual injury. Presumably our method of data collection would have missed 94% (if not all) of the cases of Tomlinson and colleagues[13] and 32% of Parks' cases.[6] It is therefore impossible to judge what fraction of *all* cases of PBP actually went on to referral to the hand clinic. The prognostic significance of our data therefore does not relate to all patients presenting immediately after operation with PBP, but rather to some subset of "worst cases". As a prognostic indicator these data are more representative of those patients with significant symptomatology 1 week after operation or at hospital discharge.

In the OHS cases of PBP the fact that all patients achieved full functional recovery in spite of this "worst case" selection suggests an extraordinarily good prognosis for this subset of cases. While most authors concur with this optimistic outlook for OHS-PBP, a prospective study of 1000 cardiac surgery patients found 55 cases of postoperative upper extremity disturbance of whom 28 recovered within several days, 19 recovered within 3 months and eight were still symptomatic 3 months after operation.[14] However, as follow-up did not extend beyond 3 months it is impossible to know the final disposition of these eight patients, and it is incorrect to assume that they suffered permanent injury. In our own series, three of eight OHS-PBP patients required 3 months or more to achieve full recovery.

Plexus injury after median sternotomy differs from PBP after NCS in several critical ways. First, PBP after OHS is far more common. As opposed to an incidence of 0.02–0.06% for NCS-PBP, the incidence of OHS-PBP in various prospective studies has ranged from a low of 1.9%[15] to 18.3%.[16] Electrophysiological evidence suggests the existence of subclinical injury in the majority of cardiac surgery patients.[17] Roy, Stafford and Charlton[18] summarized six prospective studies totalling 1772 patients undergoing OHS. The overall incidence of nerve injuries in these studies was 7.6% of which 80% (6.1%) were PBP. In their own prospective analysis of 162 cardiac surgery patients there were 12 (7.4%) cases of PBP.

OHS-PBP also differed from NCS-PBP in the distribution of the injury. Nearly all of the former involved lower roots of the plexus whereas the latter were typically lesions of the upper and middle roots. This generalization holds true throughout the literature and our data are consistent. The mechanism of injury in OHS-PBP is different (anatomically and mechanically) from that of NCS-PBP. The positioning of sternal retractors (cephalad placement promotes injury), extent of sternal retraction (excessive retraction promotes injury) and the wide, asymmetric sternal traction necessary for harvesting of an internal mammary artery graft pedicle have been associated with PBP.[14] Sternal retraction forces the clavicle into the retroclavicular space rotating the first rib superiorly and stretching the lower plexus.[19] Persistent changes in somatosensory evoked potentials associated with sternal retraction predict postoperative deficits.[20] On occasion, rib fracture may occur with the possibility of nerve penetration.[16 21] These fractures are common when evaluated by radionuclide bone scan although they are usually not detected by x-ray.[22] This mechanism may explain the more severe cases of OHS-PBP.

Another difference between OHS-PBP and NCS-PBP is in the clinical expression of the injury. Apart from the different anatomical distributions of the injuries, the presentation in NCS-PBP has been described as that of a relatively painless motor deficit which is greater in degree than sensory loss.[8] Our data supported the relative emphasis on the motor deficit in NCS-PBP. Where sensory deficit or pain–dysaesthesia presented in the NCS group it appeared to herald prolonged or incomplete recovery and an association with injury to the roots of the lower trunk in addition to those of the upper and middle trunks. For OHS-PBP the relative emphasis is on sensory disturbance as opposed to motor loss.[13 14] Our OHS-PBP patients also had primarily sensory complaints and 50% had no motor deficit.

An important difference between these two categories of PBP is that of prognosis. Although there are reported cases of persistent deficit after

OHS, the literature indicates a high likelihood of full recovery.[14 23–25] Our finding of seven patients with full recovery and one with only mild residual tingling (in spite of the "worst case" selection) is consistent with this. This compares with a less encouraging prognosis in the case of NCS-PBP.

Regarding the prognosis of OHS-PBP, most patients are already asymptomatic within several days.[13 14] In the study of Tomlinson and colleagues,[13] 94% were asymptomatic by the time of hospital discharge. Hudson, Boome and Sanpera[26] reported an incidence of 0.2% of OHS patients in their centre being referred to the hand clinic for PBP. Using the incidence data from prospective studies this implies that in their institution 96–98% of patients with OHS-PBP enjoyed rapid recovery. We estimate therefore that 90–95% of patients will be wholly or substantially improved within 1 month of surgery (with full recovery forthwith). Of those patients who have not substantially recovered by the 1 week "prognostic milestone" (our presumed criteria for referral to the hand clinic) our data suggest complete or near-complete recovery is highly likely. Most patients recover within several months, although on occasion recovery may be protracted (up to 1 yr) and, only rarely, incomplete.

In the case of NCS-PBP there are no prospective studies to allow a valid estimate of what percentage of patients have transient injury. Using the "1 week milestone" criteria, our data suggest that of those NCS-PBP patients with significant symptoms at 1 week, 79% (11 of 14) recover fully. This compares closely with Parks' finding of 82% (14 of 17 patients) full recovery. In assessing the individual patient there are no absolute markers of prognosis. However, this study suggests several possible portents to a slower recovery and worse outcome, including male gender, diabetes, injury to *all* roots of the plexus, and the presence of sensory deficit and pain or dysaesthesia. Absence of sensory recovery by 3–4 weeks and motor recovery by 6–8 weeks are further negative "prognostic milestones". Half of those patients with no motor recovery at 6–8 weeks ultimately suffered residual deficit. We stress that the data of this study are only *suggestive* and that the small number of patients involved precludes statistically significant conclusions. On the positive side, all patients achieved substantial, if not full, recovery. The role of physical therapy in this recovery cannot be overemphasized.

In summary, brachial plexus injury occurring after cardiac and non-cardiac surgery are two separate entities. The former is characterized by a predominance of sensory complaint in the lower roots of the plexus and the latter by a predominance of motor deficit in the upper and middle roots. The former is far more frequent than the latter, with an excellent prognosis for recovery. The prognosis of brachial plexopathy after non-cardiac surgery may be worse in males, diabetics, those with injury to all roots of the plexus and when, in addition to the motor deficit, there is sensory loss and pain or dysaesthesia. At a 1 week "prognostic milestone" 79% of symptomatic patients enjoyed complete recovery, although this took as long as 5 months or more in 50% of patients. In some, recovery took up to 1 yr. At the 6–8 week "prognostic milestone" 50% of those who had not yet shown evidence of improvement in the motor deficit suffered residual neurological deficit. However, all patients recovered to a significant extent even when recovery was not complete and none suffered from late deterioration or chronic pain. The relative infrequency of this serious complication and the paucity of our literature data base imply the need for further such series and perhaps ultimately their compilation through meta-analysis.

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Does the addition of clonidine affect duration of analgesia of bupivacaine wound infiltration in inguinal hernia surgery?

S. ELLIOTT, S. ECKERSALL, L. FLIGELSTONE AND S. JOTHILINGAM

Summary

We conducted a prospective, randomized, double-blind study to compare analgesia obtained by wound infiltration using 29 ml of 0.25% bupivacaine alone, or with the addition of clonidine hydrochloride 150 μg. A third group received bupivacaine wound infiltration with clonidine 150 μg i.m. to control for the systemic effects caused by absorption of clonidine. We studied 46 adults undergoing elective inguinal hernia repair. The general anaesthetic technique, postoperative analgesia and wound infiltration technique were standardized. There was no difference in time to first analgesic request or to total analgesic consumption between the three groups during the 24-h study. Visual analogue scores (VAS) at rest and after coughing were noted over a 24-h period. The only difference was higher VAS scores at rest at 24 h in the control group who received i.m. clonidine. We conclude that for elective inguinal hernia repair, postoperative analgesia obtained by bupivacaine wound infiltration was not improved by the addition of clonidine 150 μg. (*Br. J. Anaesth.* 1997; **79**: 446–449).

Key words
Sympathetic nervous system, clonidine. Anaesthetics local, bupivacaine. Anaesthetic techniques, regional. Pain, postoperative.

Clonidine hydrochloride is an $alpha_2$ adrenoceptor agonist which has long been used to treat hypertension. In anaesthesia, clonidine given systemically has been found to decrease anaesthetic and analgesic drug requirements.[1] Later it was found that when mixed with local anaesthetic, clonidine extended the duration of both the motor and sensory elements of spinal,[2] extradural,[3] axillary,[4 5] femoral[6] and intercostal[7] nerve blocks.

As the synergistic effects of clonidine and bupivacaine have been recognized in a progressively peripheral manner, we attempted to continue this progression and show if it extends to the wound itself. Therefore, the purpose of this study was to examine if clonidine mixed with bupivacaine produced significant extension of postoperative analgesia obtained by performing wound infiltration during inguinal hernia repair.

Patients and methods

We studied 46 consecutive adult patients presenting for elective unilateral inguinal hernia repair in a double-blind randomized study. The study was approved by the local Ethics Committee and Medicines Control Agency, and written informed consent was obtained from all patients. Exclusion criteria included: patients receiving alpha adrenergic blocking drugs, those with Raynaud's disease or thromboangiitis obliterans (caution is recommended as clonidine has been reported to cause a condition resembling Raynaud's phenomenon), contraindications to the general anaesthetic technique or age less than 16 yr. Operations for recurrent hernia were excluded as the degree of dissection and thus tissue trauma would be expected to be greater than for first repairs.

All patients received the same general anaesthetic. Temazepam 10–20 mg was given orally 1 h before surgery. Anaesthesia was induced with propofol 2–3 mg kg^{-1} and maintained with isoflurane and nitrous oxide in oxygen. Analgesia was provided with fentanyl 1–2 μg kg^{-1}. The airway was maintained with a laryngeal mask airway. Vecuronium was used to facilitate mechanical ventilation using a Drager Narkomed ventilator. Datex Cardiocap and Capnomac monitors were used to monitor non-invasive arterial pressure, electrocardiogram, pulse oximetry and blood-gas analysis.

Using envelope randomization, patients were allocated to one of three groups before surgery. During surgery, all patients received a 30-ml study mixture infiltrated into the wound and an i.m. injection was given by the anaesthetist into the contralateral deltoid muscle. This injection was either clonidine or saline, to control for any systemic effects of clonidine. Patients in group A underwent wound infiltration with bupivacaine 29 ml and 0.9% saline 1 ml, in addition to an i.m. injection of 0.9% saline 1 ml. Patients in group B underwent wound infiltration with bupivacaine 29 ml and clonidine 150 μg (1 ml), with an i.m. injection of 0.9% saline 1 ml.

S. ELLIOTT*, MB, CHB, FRCA, S. ECKERSALL, MB, BS, FRCA, S. JOTHILINGAM, FRCA (Department of Anaesthetics); L. FLIGELSTONE, FRCS (Department of Surgery); Lister Hospital, Stevenage, Hertfordshire SG1 4AB. Accepted for publication: May 16, 1997.

*Present address for correspondence: Department of Anaesthetics, St Marys Hospital, Praed Street, London W2 1NY.

Patients in group C had wound infiltration with bupivacaine 29 ml and 0.9% saline 1 ml, with an i.m. injection of clonidine 150 μg (1 ml). A three-stage technique of wound infiltration before each stage of dissection was devised and performed by the surgeon. First, along the proposed line of incision, skin, subcutaneous fat and tissue deep to Scarpa's fascia were infiltrated. After skin incision, further infiltration through the external oblique aponeurosis was performed. Finally, there was direct infiltration to block ilio-inguinal and ilio-hypogastric nerves, and to the deep inguinal ring. The type of hernia repair was at the surgeon's discretion.

Postoperative analgesia was provided by two co-dydramol tablets 4–6 hourly and morphine 10–15 mg i.m. 3–4 hourly if required for severe pain.

Patient randomization and preparation of the test mixture were performed by an investigator who did not act as observer subsequently. The patient, surgeon and all other medical and nursing staff were blinded to the patient's treatment. Patient data were recorded by the ward nurses and the acute pain sister, and included: time to first dose of analgesic after operation and total analgesic requirements after operation; and visual analogue pain scores (VAS) at rest and on coughing, recorded in recovery and 6 and 24 h after operation. Patients was asked to indicate the degree of pain on a 10-cm line scale without gradations, the two ends marked "no pain" and "worst imaginable pain". The type of surgical repair and duration of operation were recorded, together with any complications which required treatment.

Parametric data were expressed as mean (SD) and analysed using analysis of variance with Bonferroni multiple comparison test. Non-parametric data were expressed as median (range) and analysed using the Kruskal–Wallis test followed by Dunn's multiple comparison test. Proportional data were analysed using the chi-square test. Results were considered significant at the 5% level.

Results

Results were obtained for 46 patients; 16 patients in group A, 15 in group B and 15 in group C. The three groups were matched for age, sex, duration and type of surgery (table 1). There was no significant differences in the time to first analgesia or total analgesic consumption (table 2). There was no difference between the rate at which patients in each group first requested analgesia (fig. 1) or the number requiring no analgesia.

Although not statistically significant, the addition of clonidine to bupivacaine appeared to confer an initial advantage in terms of VAS in the initial recovery period, although this was not apparent at 6 or 24 h (table 3). The only significant difference in VAS between groups was at rest 24 h after operation when the score for group C (3.9, range 0–8.4) was significantly higher than those in groups A (2, range 0–6.6) and B (1.2, range 0–6) ($P<0.05$ Kruskal–Wallis test).

Table 1 Patient data and operative details (mean (SD or range) or number)

	Group A	Group B	Group C
Age (yr)	62.2 (16.6)	66.4 (12.7)	59.8 (17.5)
Sex (M:F)	16:0	14:1	15:0
Repair (mesh:non-mesh)	14:2	11:4	13:2
Duration of operation (min)	54.8 (15.5)	61.2 (26.5)	56.3 (20.5)

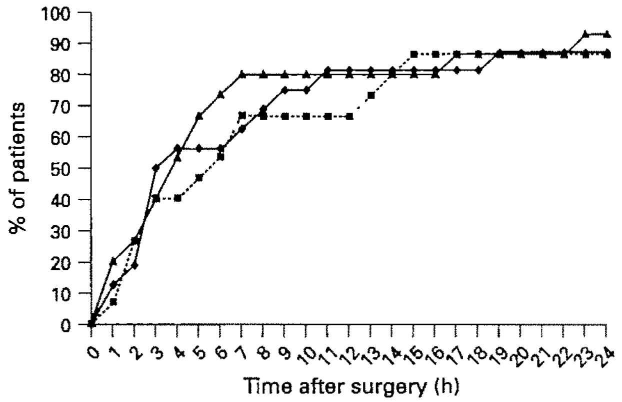

Figure 1 Percentage of patients requiring analgesia in the 24 h after inguinal hernia repair in group A (◆), group B (■) and group C (▲).

Table 2 Postoperative analgesic requirements in the first 24 h after inguinal hernia surgery. Data are median (range) except where indicated

	Group A	Group B	Group C
Total morphine (mg)	0 (0–10)	10 (0–30)	10 (0–20)
Total co-dydramol (tablets)	4 (0–6)	2 (0–8)	4 (0–6)
Time to first analgesia (min) (mean (SD))	392 (418.8)	499 (469.9)	418 (466.9)
No analgesia required	1:15	2:13	1:14

Table 3 Visual analogue scores (VAS) in the first 24 h after inguinal hernia surgery (median (range)). $^*P<0.05$ (Kruskal–Wallis)

	Group A	Group B	Group C
VAS at rest in recovery	0.85 (0–5.3)	0 (0–4.5)	2.8 (0–7)
VAS on coughing in recovery	2.1 (0–7.6)	1.3 (0–8.1)	3.55 (0–7.1)
VAS at rest 6 h postop.	1 (0–8.3)	1.6 (0–4)	1.5 (0–8)
VAS on coughing 6 h postop.	2.35 (0–8.5)	4.75 (0–6.2)	3.3 (0–9.4)
VAS at rest 24 h postop.	2 (0–6.6)	1.2 (0–6)	3.9 (0–8.4)*
VAS on coughing 24 h postop.	3.5 (0–7.5)	4.4 (0.7–10)	5.6 (1.7–10)

There was a higher incidence of adverse side effects in group C (three patients had bradycardia, associated with hypotension in two) requiring treatment with atropine and i.v. fluids. One patient in group B had bradycardia. No morbidity was noted in group A.

Discussion

We chose elective hernia surgery for this study as wound infiltration is well established as an effective method of providing postoperative analgesia[8–10] and indeed as the sole anaesthetic. The benefit of wound infiltration in other operations, for example appendicectomy, is less well demonstrated, perhaps because of the major contribution to postoperative pain of residual localized peritonitis. As there is no clear end-point to injection, we devised a standardized technique of wound infiltration which would provide a reliable distribution of local anaesthetic. This technique used pre-incisional infiltration as this has been shown to be more effective than postoperative infiltration.[11]

The addition of clonidine to local anaesthetic solutions has been shown to extend the duration of several peripheral nerve blocks. This appears to be a locally mediated effect, as it is not reproduced by systemically administered clonidine.[5] Gaumann, Brunet and Jirounek,[12] using the rabbit vagus nerve, showed that low concentrations of clonidine have an enhancing effect on lignocaine-induced inhibition of the C-fibre action potential. They suggested that this might explain the mechanism by which clonidine prolongs the action of lignocaine in peripheral nerve blocks. Singelyn, Gouverneur and Robert[4] have shown that unlike adrenaline which acts as a local vasoconstrictor, clonidine has no effect on the absorption of amide local anaesthetics from their site of action.

Although there was perhaps a trend towards improved pain scores in the immediate recovery period, we were disappointed to find that the addition of clonidine 150 μg to bupivacaine conferred no significant improvement in duration of postoperative analgesia after hernia surgery. It would appear that the conditions permitting a synergistic effect of clonidine and local anaesthetic present in major nerves are not present in the periphery. The nature of this difference is unclear and open to speculation, as there is little previous work in this area. Alternatively, the technique of wound infiltration itself may have confounded our investigation. Wound infiltration is difficult to study as, unlike neuroaxial or major nerve blocks, there is no directly measurable change in terms of motor or dermatomal block. Thus the effect of clonidine on bupivacaine wound infiltration was measured only indirectly in terms of time to first analgesia, total analgesic consumption and pain scores. It is well documented that analgesia derived from wound infiltration extends for a period far beyond the time when the local anaesthetic is present, particularly if a pre-incisional infiltration technique is used. Tverskoy and colleagues[9] demonstrated improved analgesia compared with general or spinal anaesthesia even 10 days after operation. Therefore, a possible reason for our negative findings may have been that any extension in the pharmacological action of local anaesthetic by clonidine was concealed by the prolonged analgesia provided by wound infiltration itself. It should be noted that even in control group A, the mean time to first analgesia exceeded 6 h. Infiltration of the wound produces prolonged analgesia possibly by pre-emptively blocking hyperalgesia and central nervous system hyperexcitability or "wind-up" caused by surgical trauma. Also, an anti-inflammatory action of amide local anaesthetics has been described.[13]

The only significant difference between groups was increased pain scores in group C at rest at 24 h. The relevance of this finding is questionable as 24 h is far in excess of the expected duration of action of clonidine. To confirm this finding would require further studies.

Failure to demonstrate significant differences between groups raises the possibility of type II statistical error. We conducted a *post hoc* power analysis using two assumptions. First, we considered that an important clinical difference between any two techniques would be reflected by a difference of 3.0 cm in the mean linear analogue pain scores between groups. Second, we used pooled data from the study to estimate a population SD. Using a 5% level of significance, we found that 15 patients per group yielded a power of 89%.

We used clonidine 150 μg as the majority of experience in regional anaesthesia is with this dose.[2 3 5–7] Higher doses may have revealed a peripheral effect, but may also have resulted in an increased incidence of systemic side effects.

In our hospital, hernia repair is a day surgery procedure. As our study was performed on inpatients, our study group consisted of patients with physical or social reasons requiring an overnight stay. This is reflected in the mean age of 62.7 yr in our study group. We decided to study only inpatients as clonidine is known to sometimes cause delayed sedation, hypotension and bradycardia.

In summary, addition of clonidine 150 μg to 0.25% bupivacaine wound infiltration conferred no improvement in either the quality or duration of postoperative analgesia after hernia surgery.

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Comparison of suxamethonium and different combinations of rocuronium and mivacurium for rapid tracheal intubation in children†

M. NAGUIB, A. H. SAMARKANDI, A. AMMAR AND A. TURKISTANI

Summary

The use of suxamethonium in children is associated with undesirable side effects. The synergistic effect of a rocuronium–mivacurium combination can be considered as an acceptable alternative to suxamethonium in clinical practice. The calculated ED_{50} of the rocuronium–mivacurium mixture was only 62% of the predicted value assuming a purely additive interaction. The use of this combination has not been evaluated in children. In this two-part study, we assessed the intubating conditions and pharmacodynamics of suxamethonium, rocuronium, mivacurium or a rocuronium–mivacurium combinations in children. We studied 120 ASA I children of both sexes, aged 3–10 yr. Children were premedicated with trimeprazine 2 mg kg^{-1} orally, and received fentanyl 2 μg kg^{-1} and propofol 2 mg kg^{-1} for induction of anaesthesia. They were allocated randomly to receive one of the following drugs or drug combinations: suxamethonium 1.0 mg kg^{-1}, mivacurium 0.2 mg kg^{-1}, rocuronium 0.6 or 0.9 mg kg^{-1}, mivacurium 0.1 mg kg^{-1} with rocuronium 0.3 mg kg^{-1}, or mivacurium 0.15 mg kg^{-1} with rocuronium 0.45 mg kg^{-1}. In part 1, 60 s after administration of the neuromuscular blocking drug or drug combination, tracheal intubation was performed in 60 children by mimicking rapid sequence induction, and intubating conditions were evaluated by a blinded investigator according to a standard score. In part 2, neuromuscular monitoring was established before administration of neuromuscular blocking agent(s) and the time from injection of drug or drug combination until complete ablation of T1 (onset) and recovery of T1 to 25% (duration) were recorded in another 60 children. The frequency of distribution of excellent or good intubating conditions in the higher dose of rocuronium and the combination groups were similar to those in the suxamethonium group, but significantly different ($P<0.05$) from those in the mivacurium group. Mean onset time was faster in the suxamethonium (55.1 (SD 11.4) s), rocuronium 0.9 mg kg^{-1} (70.5 (37.7) s), mivacurium 0.1 mg kg^{-1} with rocuronium 0.3 mg kg^{-1} (67 (35.9) s) and mivacurium 0.15 mg kg^{-1} with rocuronium 0.45 mg kg^{-1} (55 (26.7) s) groups compared with the mivacurium 0.2 mg kg^{-1} (116 (26.8) s) and rocuronium 0.6 mg kg^{-1} (97.9 (29) s) groups. This study demonstrated that the combination of rocuronium 0.45 mg kg^{-1} and mivacurium 0.15 mg kg^{-1} could possibly be considered as an acceptable alternative to suxamethonium when rapid sequence induction of anaesthesia is indicated in children because it provides uniform excellent intubating conditions and complete neuromuscular block in <60 s. (*Br. J. Anaesth.* 1997; **79**: 450–455).

Key words

Anaesthesia, paediatric. Interactions (drug), mivacurium. Interactions (drug), rocuronium. Neuromuscular block, suxamethonium. Neuromuscular block, mivacurium. Neuromuscular block, rocuronium. Intubation tracheal.

Because it has a brief onset of action and rapid recovery, suxamethonium is still the standard neuromuscular blocking drug for rapid sequence tracheal intubation. However, its use in children is associated with undesirable side effects[1–4] that resulted in the recent mandated changes in the suxamethonium package insert by the Food and Drug Administration.[5 6] This concern raises an important question on alternate approaches that are available to the clinician to enhance the onset of the available non-depolarizing neuromuscular blocking drugs.[7 8]

The onset of action of non-depolarizing neuromuscular blocking drugs can be accelerated by the use of high doses of an individual agent,[9 10] combinations of blockers[11] or by preceding the intubating dose with a priming dose of blocker.[12 13] These techniques, however, have not consistently achieved the rapid onset of action of suxamethonium and did not result in uniform intubating conditions matching those after suxamethonium.

Rocuronium and mivacurium are non-depolarizing neuromuscular blocking agents that have recently been introduced into clinical practice. Rocuronium has a brief onset and an intermediate

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MOHAMED NAGUIB*, MB, BCH, MSC, FFARCSI, MD, ABDULHAMID H. SAMARKANDI, MB, BS, JB, KSUF, FFARCSI, ADEL AMMAR, MB, BCH, DA, KSUF, AHMED TURKISTANI, MB, BS, Department of Anaesthesia, King Saud University, Faculty of Medicine at King Khalid University Hospital, Riyadh, Saudi Arabia. Accepted for publication: May 6, 1997.

*Address for correspondence: Department of Anaesthesiology and ICU, King Khalid University Hospital, PO Box 7805, Riyadh 11472, Saudi Arabia.

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duration of action. Mivacurium has a considerably shorter duration of action than any other currently used non-depolarizing agent. The speed of onset of rocuronium at the recommended intubating dose (0.6 mg kg^{-1}) is slower than that of suxamethonium.[10 13] Naguib[14] demonstrated that mixtures of rocuronium and mivacurium are synergistic in humans. The calculated ED_{50} of a rocuronium and mivacurium mixture (38.8 μg kg^{-1} for rocuronium and 11.4 μg kg^{-1} for mivacurium) was only 62% of the predicted value (125 μg kg^{-1} for rocuronium and 37 μg kg^{-1} for mivacurium) assuming a purely additive interaction.[14]

Because of the dangers of hyperkalaemic cardiac arrest after suxamethonium in children with unrecognized muscular dystrophy,[1–4] there have now been moves to limit the use of suxamethonium in children.[7 8] Hopkins[8] has indicated that there would be good reason not to use suxamethonium if another drug had the same advantages with fewer side effects. Therefore, the use of a rocuronium–mivacurium combination may be a reasonable alternative to suxamethonium for rapid sequence induction in children.

This two-part study was designed to assess the intubating conditions of single bolus doses of suxamethonium, rocuronium, mivacurium or different combinations of rocuronium and mivacurium in a simulated rapid sequence induction in children, and to measure onset time and duration of action of the drugs or drug combinations. This study differs from previous investigations because it included the suxamethonium group as a control, and because it compared multiple doses of rocuronium and different combinations of rocuronium and mivacurium under clinically relevant conditions.

Patients and methods

After obtaining institutional approval and informed consent from the children's parents, we studied 120 ASA I children of both sexes, aged 3–10 yr (mean 5.3 yr) and weighing 12–40 (mean 20.2 (SD 7)) kg. All patients were undergoing elective procedures, had no neuromuscular, renal or hepatic diseases, and were not receiving any drug known to interfere with neuromuscular function.

All patients received trimeprazine 2 mg kg^{-1} orally, and a local anaesthetic cream (EMLA, Astra Pharmaceuticals) was applied to the previewed puncture site 90 min before induction of anaesthesia. ECG, haemoglobin oxygen saturation by pulse oximetry (Sp_{O_2}) and arterial pressure were monitored. Temperature was monitored by a nasopharyngeal thermistor and maintained at 36.5±0.5 °C.

PART 1: RAPID SEQUENCE INDUCTION STUDY

In the first part of the study we compared the quality of neuromuscular block induced by different drugs in the context of rapid sequence induction. Sixty children were allocated randomly to one of six groups ($n=10$ in each) to receive suxamethonium 1.0 mg kg^{-1} ($2\times ED_{95}$)[15] (control group), mivacurium 0.2 mg kg^{-1} ($2\times ED_{95}$), rocuronium 0.6 mg kg^{-1} ($2\times ED_{95}$), rocuronium 0.9 mg kg^{-1} ($3\times ED_{95}$), mivacurium 0.1 mg kg^{-1} ($1\times ED_{95}$) with rocuronium 0.3 mg kg^{-1} ($1\times ED_{95}$), or mivacurium 0.15 mg kg^{-1} ($1.5\times ED_{95}$) with rocuronium 0.45 mg kg^{-1} ($1.5\times ED_{95}$). After preoxygenation with 100% oxygen for 3 min, anaesthesia was induced with fentanyl 2 μg kg^{-1} and propofol 2 mg kg^{-1} followed by the neuromuscular blocking drug or drug combination. Neuromuscular blocking drugs or drug combinations were injected over 5 s. When a combination of drugs was used, each was administered simultaneously by the same i.v. route. To maintain blinding, patients who received a single neuromuscular blocking drug had a simultaneous injection of a placebo (0.9% sodium chloride). Sixty seconds after the end of injection, the trachea was intubated in all patients by the same experienced anaesthetist who was unaware of the patient's grouping. He assessed intubating conditions using the following criteria[16]: excellent=jaw relaxed, vocal cords abducted and immobile, and no diaphragmatic movement; good=jaw relaxed, vocal cords abducted and immobile, and some diaphragmatic movement; poor=jaw relaxed, vocal cords moving, and coughing or bucking; and inadequate=jaw not relaxed and vocal cords closed. Cricoid pressure was applied during insertion of the tube. The ulnar nerve was stimulated supramaximally at the wrist with square pulses of 0.2 ms duration, delivered in a train-of-four (TOF) sequence at 2 Hz every 12 s, using a Myotest peripheral nerve stimulator (Biometer International, Odense, Denmark). The resultant contraction of the adductor pollicis muscle was evaluated by tactile assessment of thumb adduction by another investigator. The number of contractions (TOF count) felt at the time of intubation was recorded.

PART 2: PHARMACODYNAMIC STUDY

In the second part of the study we investigated the time course of neuromuscular block induced by the drugs or drug combinations. Premedication and intraoperative monitoring were similar to that described in part 1. Anaesthesia was induced in all patients with fentanyl 2 μg kg^{-1} and propofol 2 mg kg^{-1}, and the lungs were ventilated via a face mask with 70% nitrous oxide in oxygen. After induction of anaesthesia, patients received a caudal injection of plain 0.25% bupivacaine 1 ml kg^{-1}. If more than 20 ml was used, the concentration of bupivacaine was reduced to 0.1875%. End-tidal concentration of carbon dioxide was maintained at 4.8–5.3 kPa. Incremental doses of propofol were administered as necessary to maintain unconsciousness. Concentrations of nitrous oxide, oxygen and carbon dioxide were measured continuously by a multiple-gas analyser (Capnomac, Datex Instrumentarium Corporation, Helsinki, Finland).

After loss of consciousness, an acceleration transducer (Biometer International, Odense, Denmark) was fastened to the volar side of the interphalangeal joint of the thumb. The ulnar nerve was stimulated supramaximally at the wrist with square pulses of 0.2 ms duration, delivered in a train-of-four (TOF) sequence at 2 Hz every 12 s, using a Myotest peripheral nerve stimulator (Biometer International, Odense, Denmark). The resultant contraction of the adductor pollicis muscle was recorded using a neuromuscular function analyser (Myograph 2000, Biometer International, Odense, Denmark). The first twitch (T1) of the TOF was considered the twitch height. The test hand was immobilized in a supine position using an arm board. Free movement during evoked thumb adduction was allowed by fixation of the extended four ulnar fingers by adhesive tape.

After a stable neuromuscular response was obtained, 60 children were allocated randomly to one of six groups ($n=10$ in each) to receive suxamethonium (control group), mivacurium, rocuronium, or a mivacurium–rocuronium combination in doses similar to those described in part 1. All drugs were administered as a single bolus dose over 5 s. When a combination of drugs was used, each was administered simultaneously by the same i.v. route. Tracheal intubation was performed at maximum block. Intubating conditions were not assessed in this part of the study. The times from injection of neuromuscular blocking drug or drug combination to complete ablation of T1 (onset time), from injection to recovery of T1 to 25% of baseline (clinical duration of action) and from recovery of T25–T75% (recovery index) were recorded.

In patients who received suxamethonium or mivacurium, a blood sample was obtained from an antecubital vein in the arm contralateral to that used for i.v. fluid administration for measurement of plasma cholinesterase (PCHE) activity, dibucaine and fluoride numbers. Plasma cholinesterase activity was measured by the change in absorbance at 600 nm after reduction of butyrylthiocholine to thiocholine, using BM/Hitachi 917, Boehringer Mannheim Diagnostics (Mannheim, Germany).

Intubating conditions were analysed by the Kruskall–Wallis test after assigning a numeric value to each intubation score. Dunnett's test was used to compare the suxamethonium (control) group with each of the other groups. Comparisons between groups who received rocuronium, mivacurium or a combination were carried out using the Student–Newman–Keuls multiple range test. Statistical analyses were carried out using BMDP statistical software (v. 7.01, University of California Press, Berkeley, CA, 1993). Results are expressed as mean (SD), and were considered statistically significant when $P<0.05$.

Results

There were no significant differences in distribution of age, weight or sex ratio between the groups (tables 1, 2). Similarly, dibucaine and fluoride numbers and baseline activity of PCHE were similar in all groups.

PART 1: RAPID SEQUENCE INDUCTION STUDY

The frequency of distribution of excellent or good intubating conditions in the higher dose of rocuronium and the combination groups were similar to those in the suxamethonium group, but significantly different ($P<0.05$) from those observed in the mivacurium group (table 1).

The number of TOF count felt at the time of intubation was significantly greater in the mivacurium, rocuronium 0.6 mg kg^{-1} and mivacurium 0.1 mg kg^{-1}–rocuronium 0.3 mg kg^{-1} groups compared with the suxamethonium group ($P<0.01$; Dunnett's test), rocuronium 0.9 mg kg^{-1} group or the mivacurium 0.15 mg kg^{-1}–rocuronium 0.45 mg kg^{-1} combination group ($P<0.05$; Student–Newman–Keuls multiple range test) (table 1).

Table 1 Rapid sequence induction study. Patient data (mean (SD) [range]) and intubating conditions ($n=10$ in each group). TOF count was measured at the time of tracheal intubation. *$P<0.05$ *vs* mivacurium group (Kruskall–Wallis test); †$P<0.01$ *vs* suxamethonium group (Dunnett's mean comparison between the control group and other groups); ‡$P<0.05$ *vs* other groups (Student–Newman–Keuls multiple range test for groups that received rocuronium, mivacurium or their combinations)

				Intubating conditions at 60 s							
Group	Age (yr)	Weight (kg)	Sex (M/F)	Excellent	Good	Poor	Inadequate	TOF count	PCHE activity (u.ml^{-1}) (Reference range 3.5–13 u.ml^{-1})	Dibucaine number	Fluoride number
Suxamethonium 1.0 mg kg^{-1}	5.1 [3–8]	20.1 (7.1) [13.5–34]	7/3	9	1	0	0	0.4 (0.7) [0–2]	9.4 (1.5) [7.8–13]	88.9 (2.2) [86–94]	47.4 (1.9) [44–50]
Mivacurium 0.2 mg kg^{-1}	5.7 [3–10]	24 (10.1) [13–40]	8/2	5	4	1	0	4 (0)† [4]	8.9 (1.2) [6.7–10.9]	88.9 (1.6) [86–91]	49.1 (3.5) [45–55]
Rocuronium 0.6 mg kg^{-1}	4.4 [3–7]	16.7 (2.8) [13–21]	7/3	7	3	0	0	3.5 (0.8)† [2–4]	—	—	—
Rocuronium 0.9 mg kg^{-1}	5.5 [3–9]	22.8 (6.5) [14–35]	7/3	10*	0	0	0	0.8 (1.1)‡ [0–3]	—	—	—
Mivacurium 0.1 mg kg^{-1} + rocuronium 0.3 mg kg^{-1}	5.5 [3–10]	18.4 (4.9) [13–30]	8/2	9	1	0	0	2.4 (1.8)† [0–4]	9.3 (1.8) [7.4–12.4]	88.2 (1.5) [86–90]	47.9 (2.7) [47–55]
Mivacurium 0.15 mg kg^{-1} + rocuronium 0.45 mg kg^{-1}	5.6 [3–10]	19.4 (7.3) [12–34]	6/4	10*	0	0	0	1.2 (1.7)‡ [0–4]	9.9 (1.5) [7.4–12.9]	88.3 (1.2) [86–90]	46.7 (1.7) [44–49]

Table 2 Pharmacodynamic study. Patient, onset and recovery data (mean (SD) [range]) (n=10 in each group). Onset time=time interval between completion of injection of the neuromuscular blocking drug or drug combination and time to maximal depression of T1; Duration=time interval between completion of injection of the neuromuscular blocking drug or drug combination and time to T1 recovery to 25% of control; recovery index=time from T25% to T75% of recovery. *$P<0.05$, **$P<0.01$ *vs* suxamethonium group (Dunnett's mean comparison between the control group and other groups); †$P<0.05$ *vs* other groups (Student–Newman–Keuls multiple range test for groups that received rocuronium, mivacurium or their combinations)

Group	Age (yr)	Weight (kg)	Sex (M/F)	PCHE activity (u.ml^{-1}) (Reference range 3.5–13 u.ml^{-1})	Dibucaine number	Fluoride number	Onset time (s)	Duration (min)	Recovery index (min)
Suxamethonium	5.9	19.2 (4.8)	8/2	9.5 (1.3)	88.8 (1.7)	48.3 (2.1)	55.1 (11.4)	4.2 (1.4)	1.3 (0.4)
1.0 mg kg^{-1}	[4–9]	[13.5–28.5]		[8–11.4]	[87–92]	[45–52]	[35–75]	[2.2–6.5]	[0.7–1.7]
Mivacurium	5.6	19 (6.8)	7/3	9.4 (1.8)	88.1 (1.5)	46.7 (1.3)	116 (26.8)**†	10.4 (1.5)*	4.2 (0.7)*†
0.2 mg kg^{-1}	[3–10]	[12–33]		[6.9–11.9]	[85–90]	[45–49]	[85–160]	[8.1–12.4]	[3.3–5.7]
Rocuronium	5.9	21.1 (7.7)	9/1	—	—	—	97.9 (29)**†	23.7 (5.1)**†	9.2 (3.1)**
0.6 mg kg^{-1}	[3.5–10]	[15–37]					[52–150]	[15.8–32]	[5.6–16.5]
Rocuronium	5.7	19.1 (5.1)	8/2	—	—	—	70.5 (37.7)	36.4 (7.4)**†	10.1 (3.1)**
0.9 mg kg^{-1}	[3–9]	[14–27.5]					[38–150]	[24.8–45.1]	[4.2–14.9]
Mivacurium	5.5	18.7 (7.3)	8/2	9.8 (1.5)	87.5 (1.2)	46.7 (1.3)	67 (35.9)	15.2 (3.8)**	7.3 (1.8)**
0.1 mg kg^{-1} + rocuronium 0.3 mg kg^{-1}	[3–10]	[12–36]		[7.8–12.5]	[85–89]	[45–49]	[40–120]	[10–22]	[4.3–10.4]
Mivacurium	5.8	19 (4.8)	8/2	9.6 (1.3)	88.2 (1.7)	47.2 (1.4)	55 (26.7)	25.3 (4.6)**†	9.9 (2.4)**
0.15 mg kg^{-1} + rocuronium 0.45 mg kg^{-1}	[3–9]	[13.5–27.5]		[7.8–11.5]	[85–91]	[45–49]	[31–110]	[18.3–35.1]	[7.4–14.9]

PART 2: PHARMACODYNAMIC STUDY

Onset time was faster in the suxamethonium 1.0 mg kg^{-1}, rocuronium 0.9 mg kg^{-1} and combination groups compared with the mivacurium 0.2 mg kg^{-1} and rocuronium 0.6 mg kg^{-1} groups (table 2). Clinical duration and recovery index were shortest in the suxamethonium group compared with all other groups ($P<0.05$ or less). In patients who received non-depolarizing neuromuscular blocking drugs or drug combinations, clinical duration was longest in the rocuronium 0.9 mg kg^{-1} group ($P<0.05$) and shortest in the mivacurium 0.2 mg kg^{-1} group and mivacurium 0.1 mg kg^{-1}–rocuronium 0.3 mg kg^{-1} combination group ($P<0.05$). Recovery index was shortest ($P<0.05$) in the mivacurium group compared with the other groups who received rocuronium or drug combinations.

Discussion

We have assessed for the first time the potential of different doses of rocuronium and different combinations of rocuronium and mivacurium for rapid sequence induction in children compared with suxamethonium. This study demonstrated that children who received the combination of mivacurium 0.15 mg·kg^{-1} and rocuronium 0.45 mg kg^{-1} were similar to those who received suxamethonium in having uniform excellent tracheal intubating conditions and an onset of complete paralysis of <60 s. However, clinical duration of neuromuscular block was six times as long in the former group ($P<0.01$) compared with the suxamethonium group (25.3 (4.6) min *vs* 4.2 (1.4) min, respectively). In addition, a much larger SD for onset times was noted in the mivacurium–rocuronium combination groups compared with that after suxamethonium.

In part 1 of this study, we followed the strict clinical procedure of rapid sequence induction. Drugs that influence intubating conditions,[12 17 18] such as volatile anaesthetics, opioids or hypnotics, were not given to our patients after administration of the neuromuscular blocking drug or drug combination. In our patients, anaesthesia was induced with propofol. Although it has been suggested that propofol produces greater depression of pharyngeal and laryngeal reactivity than thiopentone,[19] this finding has not been substantiated by others.[18 20] In our study, the tracheas of all children were intubated successfully within 60 s after administration of the neuromuscular blocking drug or drug combination, and intubating conditions did not differ in patients who received either suxamethonium, rocuronium 0.9 mg kg^{-1} or the higher dose of the combination groups (table 1). Rocuronium 0.6 mg kg^{-1} did not produce as good intubating conditions as suxamethonium 1.0 mg kg^{-1} after 60 s. We noted also that mivacurium 0.2 mg kg^{-1} was not suitable for rapid tracheal intubation in children (table 1). Similar observations were reported by others even when doses up to mivacurium 0.3 mg kg^{-1} were administered in children.[21] Our results are in accordance with those reported by Fuchs-Buder and Tassonyi in children in whom tracheal intubation was carried out by mimicking rapid sequence induction.[16] They noted excellent intubating conditions in 83% and 94% of patients, 60 s after rocuronium 0.6 mg kg^{-1} and 0.9 mg kg^{-1}, respectively.[16] Woelfel and colleagues[22] found that intubating conditions 60 s after rocuronium in 12 children during steady state halothane anaesthesia were excellent in nine and good in three patients.

We found that complete neuromuscular block at the adductor pollicis muscle was not a prerequisite for optimal intubating conditions. In our study tracheal intubation was performed 60 s after administration of the neuromuscular blocking drug or drug combination, regardless of the degree of neuromuscular block. In adults, faster onset at the laryngeal compared with the peripheral muscles has been reported with suxamethonium, rocuronium and mivacurium.[23–25] However, the onset of action of rocuronium at the laryngeal adductor muscles is slower than that after suxamethonium, and the degree of block is less intense.[26] In this study, onset time in the rocuronium 0.9 mg kg^{-1} group was similar to that in the suxamethonium group (table 2). As the dose of rocuronium increased from 0.6 to 0.9 mg kg^{-1}, onset time for neuromuscular block decreased by 28% (from 97.9 to 70.5 s; $P<0.05$) and duration of action increased by 55% (from 23.7 to 36.4 min; $P<0.05$) (table 2). This was associated with a concomitant increase in the recovery index (table 2). Using electromyography (Relaxograph) during isoflurane anaesthesia, Fuchs-Buder and Tassonyi[16] demonstrated that increasing the dose of rocuronium from 0.6 to 0.9 mg kg^{-1} in children significantly decreased onset time (193 (47) *vs* 118 (23) s) and prolonged clinical duration (21 (4) *vs* 34 (11) min). In the latter study,[16] however, the investigators re-calibrated the Relaxograph after administration of rocuronium when steady state concentrations of the volatile anaesthetic were achieved.

The results of our study confirm our previously published data in adults that combinations of rocuronium and mivacurium produced a shorter onset time comparable with that of suxamethonium.[14] In this study, time to maximal neuromuscular block decreased from 97.9 to 67 s ($P<0.05$) and both clinical duration and recovery index decreased from 23.7 and 9.2 min to 15.2 ($P<0.05$) and 7.3 min, respectively, when rocuronium 0.3 mg kg^{-1} together with mivacurium 0.1 mg kg^{-1} were given instead of rocuronium 0.6 mg kg^{-1} alone. The clinical profile of this combination was similar to that reported with equipotent doses in adults (rocuronium 0.3 mg kg^{-1} and mivacurium 0.075 mg kg^{-1}) with respect to onset time (69 s) and recovery index (7.5 min).[14] However, the clinical duration was different—15.2 min in children (this study) *vs* 34 min in adults.[14] There may be pharmacokinetic reasons for the differences between adults and children. The pharmacokinetics of rocuronium in children aged 4–11 yr revealed an age-dependent increase in plasma clearance[27] that contributed to the shorter duration of action compared with infants or adults.[28] The increased cardiac output in children may also contribute to the shortened duration of action by removing the drug from the neuromuscular junction more rapidly than in adults.[29] These pharmacokinetic differences could explain the longer clinical duration of the rocuronium–mivacurium combination observed in adults compared with children.

We also noted that increasing the dose of the components in the combination—as in the rocuronium 0.45 mg kg^{-1}–mivacurium 0.15 mg kg^{-1} combination—resulted in a 44% and 22% shorter onset time than that produced by rocuronium 0.6 and 0.9 mg kg^{-1}, respectively (55 *vs* 97.9 and 70.5 s, respectively). The clinical duration observed with the latter combination (25.3 min) was similar to that seen with rocuronium 0.6 mg kg^{-1} (23.7 min), but was 30% shorter ($P<0.05$) than that noted with rocuronium 0.9 mg kg^{-1} (36.4 min) (table 2).

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Effect of temperature and cardiopulmonary bypass on the pharmacokinetics of remifentanil

D. RUSSELL, D. ROYSTON, P. H. REES, S. K. GUPTA AND G. N. C. KENNY

Summary

Sixteen patients undergoing coronary revascularization requiring cardiopulmonary bypass received remifentanil 2 μg kg^{-1} or 5 μg kg^{-1} by infusion over 1 min after sternotomy but before commencing cardiopulmonary bypass, during hypothermic cardiopulmonary bypass and during cardiopulmonary bypass after rewarming. Hypothermic cardiopulmonary bypass reduced the clearance of remifentanil by an average of 20%, and this was attributed to the effect of temperature on blood and tissue esterase activity. Reductions in arterial pressure occurred with administration of both doses during normothermia only. (*Br. J. Anaesth.* 1997; **79**: 456–459).

Key words
Analgesics opioid, remifentanil. Pharmacokinetics, remifentanil. Heart, cardiopulmonary bypass. Temperature, effect. Surgery, cardiovascular.

Infusions of fentanyl, alfentanil and sufentanil have become established for use during induction and maintenance of anaesthesia in patients undergoing cardiac and vascular surgery.[1–3]

Remifentanil hydrochloride is a synthetic mu receptor agonist with an analgesic potency similar to that of fentanyl,[4] but with an ultra-short duration of action because of rapid hydrolysis by plasma and tissue esterases. Westmoreland and colleagues[5] investigated the pharmacokinetics of remifentanil in 24 ASA I–III patients undergoing elective surgery. They administered remifentanil 2, 5, 15 or 30 μg kg^{-1} over 1 min, and concluded that its pharmacokinetics were best described by a three-compartment model. The initial distribution half-life was approximately 30 s, intermediate disposition half-life 2–4 min and terminal half-life 10–20 min. Clearance was 250–300 litre h^{-1} (4.17–5 litre min^{-1}) and was independent of the dose of remifentanil administered, sex, body weight or age. Mean volume of distribution at steady state was 24.3–39.8 litre, with approximately 20% of this attributable to the central compartment.

GR90291, the major carboxylic acid metabolite of remifentanil, has 0.02% the potency of its parent molecule and is eliminated primarily by the kidneys.[6] Its pharmacokinetics have been shown to be linear, with a mean terminal half-life of 88.1–137.4 min.[5]

Dershwitz and colleagues[7] administered remifentanil 1 μg kg^{-1} over 1 min followed by infusion of 0.05–1.0 μg $kg^{-1}min^{-1}$ until the end of surgery in 29 patients after induction of anaesthesia with propofol. Despite the variation in infusion rate, the times to onset of spontaneous respiration after discontinuation of remifentanil were similar, suggesting that remifentanil was not rate limiting in recovery from anaesthesia.

Remifentanil might therefore be attractive for use in circumstances where varying degrees of intense opioid activity are required, and where after discontinuation of infusion of opioid, blood concentrations, and hence opioid receptor occupancy, decrease rapidly and predictably irrespective of the dose or duration of infusion. Another potentially attractive feature is that the pharmacokinetics of remifentanil are unlikely to be affected significantly by hepatic[8 9] or renal impairment.[10]

Esmolol is a short-acting β-adrenergic blocking agent which is metabolized extensively by esterases present in the cytosol of red blood cells.[11] Kramer and colleagues[12] investigated the pharmacokinetics of esmolol in patients undergoing cardiac anaesthesia and observed that clearance was reduced during hypothermic cardiopulmonary bypass (CPB). They attributed this to reduced enzymatic hydrolysis associated with hypothermia, and as remifentanil undergoes hydrolysis by similar enzyme systems we hypothesized that similar principles might apply. This might significantly affect remifentanil requirements during hypothermic CPB. The aim of this study was to assess the effect of temperature and CPB on the pharmacokinetics and pharmacodynamics of remifentanil in patients undergoing coronary revascularization.

D. RUSSELL, FRCA, University Department of Anaesthesia, Royal Infirmary, Glasgow G31 2ER. D. ROYSTON, FRCA, MD, Department of Anaesthesia, Harefield Hospital, Harefield, Middlesex UB9 6JH. P. H. REES, BSC, PHD, Glaxo Wellcome Research and Development, Greenford, Middlesex UB6 0HE. S. K. GUPTA, PHD, Department of Clinical Pharmacology, Glaxo Wellcome Research Institute, North Carolina, USA. G. N. C. KENNY, BSC(HONS), FRCA, MD, University Department of Anaesthesia, Royal Infirmary, Glasgow G31 2ER. Accepted for publication: May 2, 1997.

Correspondence to G. N C. K.

Patients and methods

After obtaining Ethics Committee approval, 16 male or female patients, aged 18–65 yr, undergoing elective coronary revascularization requiring CPB gave written informed consent to take part in the study. Exclusion criteria were a recent history of unstable angina or myocardial infarction, significant left main stem coronary artery disease, significant valvular heart disease, significant hepatic or renal disease, recent history of major opioid use, personal or family history of cholinesterase deficiency and obesity (greater than 25% above ideal weight for height).

Concomitant cardiovascular medication was continued up to and including the day of surgery. Patients received benzodiazepine–opioid premedication and anaesthesia was induced and maintained using an opioid–hypnotic–neuromuscular blocker technique. In all cases the CPB pump was primed with 2 litre of crystalloid, diastolic cardiac arrest was induced with cold crystalloid cardioplegia, and during CPB arterial blood pH was maintained at 7.4 (measured at 37 °C).

REMIFENTANIL ADMINISTRATION

Remifentanil was delivered from a motorized syringe driver over 60 s via a central venous catheter into the superior vena cava. Each patient was scheduled to receive three i.v. bolus doses of remifentanil, at distinct times during surgery.

Period A (normothermic, pre-bypass) after sternotomy but before commencing CPB, with a core (nasopharyngeal) temperature >35 °C.

Period B (hypothermic, on bypass) during hypothermic CPB, with a core temperature of 28–30 °C for at least 15 min.

Period C (normothermic, on bypass) before discontinuation of CPB, with a core temperature of >36 °C for at least 5 min.

The study had a dose escalation design, with the first eight patients receiving three bolus doses of 2 μg kg^{-1}, and the remaining eight patients receiving three doses of 5 μg kg^{-1}. Haemodynamic indices were recorded during the period immediately after administration of remifentanil.

SAMPLE COLLECTION AND ANALYSIS

Blood samples (5 ml) were obtained from a radial artery cannula immediately before administration of remifentanil, and at 1, 2, 3, 4, 5, 10, 15, 20 and 30 min after the start of administration or until the criteria for periods A, B or C no longer applied (mainly discontinuation of CPB). The samples were heparinized and two duplicate 2.5-ml aliquots were placed in tubes containing 50 μl of 50% citric acid. Each tube was vortexed vigorously for 10 s, inverted several times and frozen at −20 °C. Concentrations of remifentanil in whole blood were measured by GC high resolution mass spectrometry, with a lower limit of detection of 0.1 ng ml^{-1}. The inter-day coefficient of variation was less than 8.5% at 0.25 ng ml^{-1}, and 4.6% at 80 ng ml^{-1}.

Compartmental data analysis involved fitting the blood concentration–time data for each phase to a two- or three-compartment model with zero order input rate using the non-linear least squares regression analysis program PCNONLIN.[13] A weighting scheme of $1/C_{\text{predicted}}$ was used. The choice of $1/C_{\text{predicted}}$ rather than $1/C_{\text{observed}}$ was made because we believe that the true variance of the observations (and hence the weighting) is estimated better from the entire data set (the model predicted values) than from an individual observation. Model selection was based on the following goodness of fit measures: visual inspection of the residual plots, magnitude of the standard error of variable estimates and Akaike's information criteria.[14]

Comparison between dose groups (2 and 5 μg kg^{-1}) was conducted using the two sample *t* test (SAS PROC TTEST) on un-transformed and log-transformed variables, and with a non-parametric method (Wilcoxon Rank Sum, SAS PROC NPAR/WA). Treatment group comparisons (normothermia pre-bypass compared with hypothermic CPB) were conducted using analysis of variance of un-transformed data (SAS PROC GLM).

Results

PHARMACOKINETIC DATA

The pharmacokinetics of remifentanil 2 μg kg^{-1} were determined in eight patients during period A (pre-bypass, normothermia), in seven patients during period B (CPB, hypothermia) and in four patients during period C (CPB, normothermia) (table 1). Results were obtained in eight, seven and

Table 1 Mean (SD) pharmacokinetic variables following administration of remifentanil 2 μg kg^{-1} during period A (pre-bypass, normothermia), period B (cardiopulmonary bypass (CPB), hypothermia) and period C (CPB, normothermia). $t_{1/2}^{\lambda 1}$=distribution half-life, $t_{1/2}^{\lambda 2}$=elimination half-life, V_1=volume of distribution (central compartment), V^{SS}=volume of distribution at steady state, *Cl*=clearance.

	Period A (n=8)	Period B (n=7)	Period C (n=4)
$t_{1/2}^{\lambda 1}$ (min)	0.6 (0.19)	0.8 (0.65)	0.7 (0.16)
$t_{1/2}^{\lambda 2}$ (min)	6.2 (0.81)	13.8 (10.2)	9.2 (1.54)
V_1 (ml kg^{-1})	82 (63.5)	109 (144.0)	161 (124.0)
V^{SS} (ml kg^{-1})	221 (115.0)	456 (606.0)	381 (312.0)
Cl (ml min^{-1}kg^{-1})	37 (15.6)	28 (8.78)	41 (26.9)

Table 2 Mean (SD) pharmacokinetic variables following administration of remifentanil 5 μg kg^{-1} during period A (pre-bypass, normothermia), period B (cardiopulmonary bypass (CPB), hypothermia) and period C (CPB, normothermia) $t_{1/2}^{\lambda 1}$=distribution half-life, $t_{1/2}^{\lambda 2}$=elimination half-life, V_1=volume of distribution (central compartment), V^{SS}=volume of distribution at steady state, *Cl*=clearance.

	Period A (n=8)	Period B (n=7)	Period C (n=6)
$t_{1/2}^{\lambda 1}$ (min)	0.6 (0.21)	0.8 (0.38)	0.5 (0.18)
$t_{1/2}^{\lambda 2}$ (min)	6.7 (2.42)	10.0 (3.27)	6.0 (2.02)
V_1 (ml kg^{-1})	39 (13.6)	64 (78.4)	40 (24.0)
V^{SS} (ml kg^{-1})	132 (44.6)	201 (147.0)	156 (90.4)
Cl (ml min^{-1}kg^{-1})	26 (8.3)	22 (9.7)	30 (6.8)

Table 3 Mean (SD) combined pharmacokinetic variables following administration of remifentanil 2 and 5 μg kg^{-1} during period A (pre-bypass, normothermia), period B (cardiopulmonary bypass (CBP), hypothermia) and period C (CBP, normothermia). $t_{1/2}^{\lambda1}$=distribution half-life, $t_{1/2}^{\lambda2}$=elimination half-life, V_1=volume of distribution (central compartment), V^{SS}=volume of distribution at steady state, Cl=clearance. **P*=0.0057 compared with period A (analysis of variance)

	Period A (n=16)	Period B (n=14)	Period C (n=10)
$t_{1/2}^{\lambda1}$ (min)	0.6 (0.19)	0.8 (0.51)	0.6 (0.22)
$t_{1/2}^{\lambda2}$ (min)	6.4 (1.76)	11.9 (7.51)	7.2 (2.40)
V_1 (ml kg^{-1})	61 (49.6)	86 (113.9)	89 (96.3)
V^{SS} (ml kg^{-1})	1767 (96.2)	329 (443.4)	246 (224.6)
Cl (ml min^{-1} kg^{-1})	32 (13.4)	25 (9.1)*	35 (17.2)

six patients receiving remifentanil 5 μg kg^{-1} during periods A, B and C, respectively (table 2). Remifentanil concentrations immediately before the doses administered during bypass were at or below the limit of analytical detection and were therefore considered to be zero. The fraction AUC extrapolated using the two-compartment terminal elimination rate constant was less than 20%.

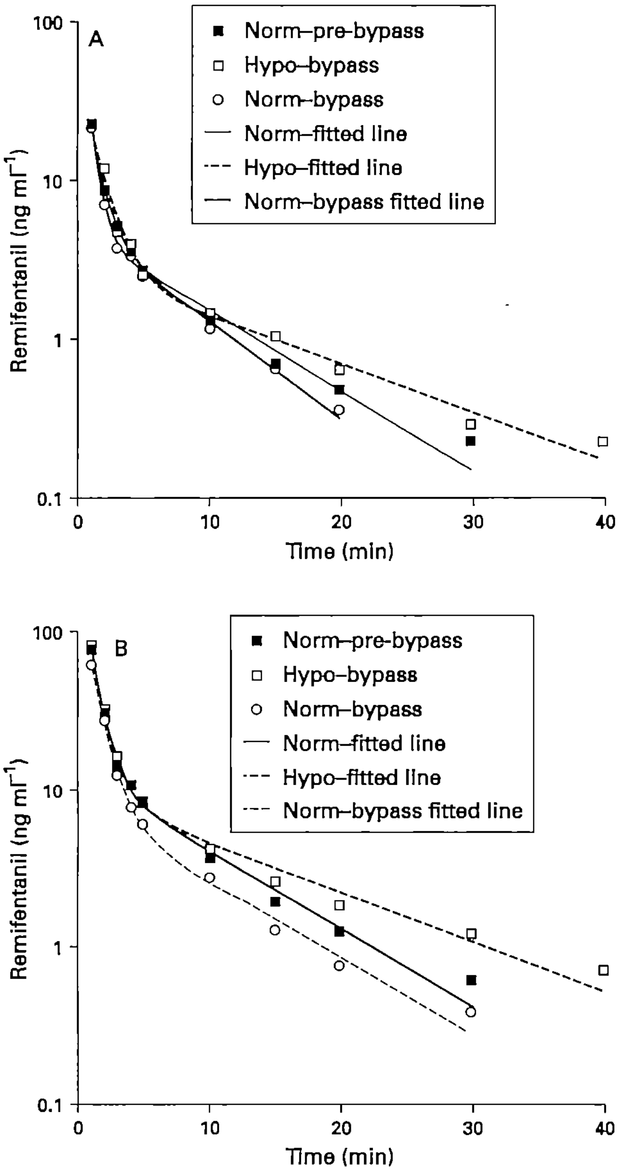

Figure 1 A: Mean blood concentration–time profiles after administration of remifentanil 2 μg kg^{-1}. B: Mean blood concentration–time profiles after administration of remifentanil 5 μg kg^{-1}.

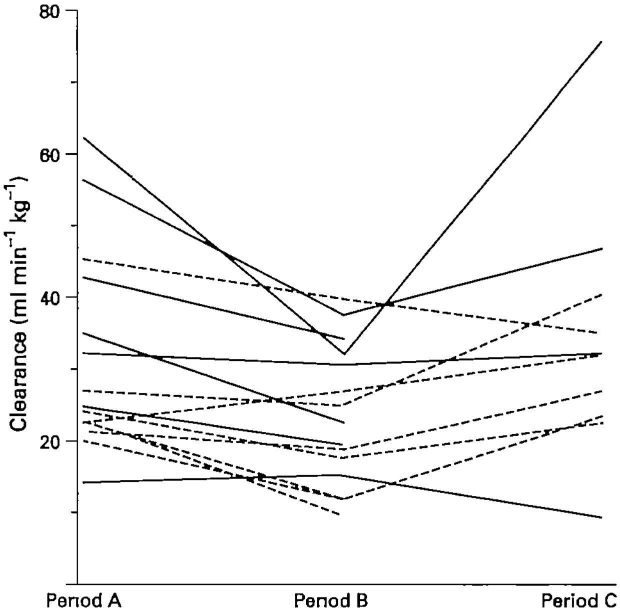

Figure 2 Clearance of remifentanil after administration of 2 μg kg^{-1} (---) and 5 μg kg^{-1} (——) during period A (pre-bypass, normothermia), period B (cardiopulmonary bypass (CPB), hypothermia) and period C (CPB, normothermia).

Blood remifentanil concentration–time profiles were fitted to a two- or three-compartment pharmacokinetic model. Statistical evaluation of the goodness of fit demonstrated that the three-compartment model offered no significant improvement over the two-compartment model. Therefore, the data were represented by a two-compartment model for further comparison between dose groups and treatment periods.

There were no significant differences in the pharmacokinetics of remifentanil between the two dose groups (ANOVA; $P>0.05$). Data for the two groups were therefore pooled and are shown in table 3. Mean blood concentration–time profiles for the two doses are shown in figure 1A and 1B. Clearance of remifentanil was similar in periods A and C (fig. 2), but was reduced by an average of 20% during period B compared with period A in the same individuals (ANOVA; $P=0.0057$). This was attributed to reduced hydrolytic enzyme activity at the lower temperatures associated with hypothermic CPB. No significant difference in volume of distribution at steady state (V^{ss}) was detected between treatment periods.

HAEMODYNAMIC DATA

Brief reductions in arterial pressure of 14–25% occurred during periods A (fig. 3) and C after administration of remifentanil 2 and 5 μg kg^{-1}. Mean arterial pressure was unchanged during period B with both doses. No clinically relevant alterations in heart rate occurred with administration of remifentanil at either dose.

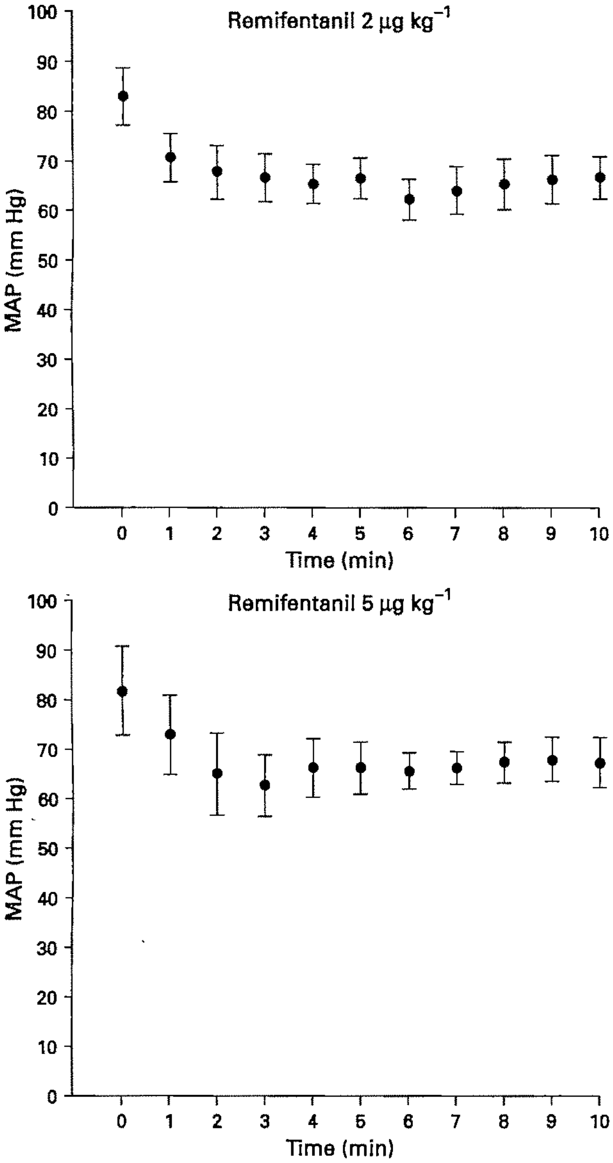

Figure 3 Mean (SD) mean arterial pressure (MAP) after administration of remifentanil 2 or 5 μg kg^{-1} during the period between sternotomy and commencing cardiopulmonary bypass. Remifentanil was administered over 60 s between 0 and 1 min.

Discussion

The mean value for clearance of remifentanil in the 2-μg kg^{-1} dose group was consistent with that observed in previous studies, while the value observed after administration of 5 μg kg^{-1} was somewhat lower than typically seen. Previous studies[5,15] with remifentanil have demonstrated linear pharmacokinetics over a wide range of doses in both healthy volunteers and anaesthetized patients. Therefore, we believe that the lower clearance in the 5-μg kg^{-1} group reflected inter-patient variability in a study of this nature using eight patients in each group, rather than being caused by dose-dependent (non-linear) pharmacokinetics. As such, we considered using pooled data from the two groups to be appropriate. The pooled dose group analysis was consistent with the individual group analyses and demonstrated a modest, but consistent, reduction in remifentanil clearance during hypothermic CPB compared with matched pre-bypass values.

As the pharmacokinetics of remifentanil were only modestly altered by hypothermic CPB, administration of remifentanil during cardiac anaesthesia can therefore be based on anticipated or observed patient need without the concern for major dosage adjustment during bypass.

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Influence of pulse oximeter lower alarm limit on the incidence of hypoxaemia in the recovery room†

A. T. RHEINECK-LEYSSIUS AND C. J. KALKMAN

Summary

In a prospective, randomized study, we have investigated the effects of two arbitrary pulse oximeter lower alarm limit (LAL) settings (90%=group 90, n=320 and 85%=group 85, n=327) on the incidence of hypoxaemia in the recovery room. In group 90, we calculated the theoretical effect of elimination of transient episodes of low pulse oximeter oxyhaemoglobin saturation (Sp_{O_2}) by introducing a time delay between the onset of the alarm condition and triggering of the alarm. When only hypoxaemic episodes lasting more than 1 min were included, Sp_{O_2} ≤90% occurred in 11% of patients in group 90 and in 20% in group 85 (relative risk (RR) 1.84, confidence interval (CI) 1.26–2.69; P<0.01). Hypoxaemia ≤85% occurred in 2% of patients in group 90 and in 6% in group 85 (RR 3.10, CI 1.32–7.28; P<0.01). In group 90, 1007 alarms (33% false) occurred, whereas in group 85, 395 alarms (28% false) occurred. Introducing a theoretical delay of 15 s in group 90 between crossing the alarm threshold and triggering the alarm would have reduced the number of alarms by 60%. The results of the study suggest that decreasing the alarm limit in an attempt to reduce frequent false alarms may lead to an increase in more relevant episodes of hypoxaemia and setting the LAL at 85% cannot be recommended routinely. Introducing a 15 s delay in group 90 would reduce the number of alarms by the same amount as changing the LAL from 90% to 85%. (*Br. J. Anaesth.* 1997; **79**: 460–464).

Key words
Equipment, alarms. Oxygen, saturation Hypoxaemia. Equipment, pulse oximeters.

The rationale for pulse oximetry monitoring is the expectation that early recognition of hypoxaemia prevents critical respiratory events.[1 2] Because respiratory problems are common in the initial postoperative period, pulse oximetry monitoring has been accepted universally as a standard of care to alert personnel in the recovery room to impending hypoxaemia. Audible alarms have been incorporated in these monitors to anticipate or detect critical situations in an environment in which personnel must perform multiple tasks. An average frequency of pulse oximeter alarms in the recovery room of once every 8 min has been reported.[3] Another study showed that only 10% of alarms were clinically relevant.[4] Frequent clinically insignificant alarms have the potential to frustrate personnel, distract attention from more important tasks and can even result in unnecessary therapeutic interventions, neglect of true alarms or permanent disabling of the alarm.[5]

It is obvious that decreasing the pulse oximeter lower alarm limit (LAL) should reduce the number of alarms. However, it is uncertain if this would reduce its efficacy as a monitor of impending severe hypoxaemia. For sudden severe events there might be little difference. For example, when pulse oximeter oxyhaemoglobin saturation (Sp_{O_2}) decreases rapidly after the onset of respiratory arrest, the triggering of an alarm by an Sp_{O_2} of 90% or 85% may be only marginally different. None the less, many clinicians argue that decreasing the alarm limit might increase the incidence of hypoxaemia. The effects of LAL on the incidence and duration of hypoxaemia have not been evaluated. In a prospective, randomized study, we have investigated the effects of two arbitrary LAL settings (Sp_{O_2} 90% and 85%) on the incidence and duration of hypoxaemia in the recovery room. As an alternative to a LAL of 85%, the effect of maintaining the LAL at 90% and elimination of short-lasting alarms by introducing an alarm delay (a delay between Sp_{O_2} crossing the alarm threshold and triggering of the audible alarm) was calculated.

Patients and methods

We studied consecutive patients who entered the recovery room of a regional (non-teaching) hospital after general or regional anaesthesia over a 1-month period. The study was approved by the hospital

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AART T. RHEINECK-LEYSSIUS*, MD, COR J. KALKMAN‡, MD, Department of Anaesthesia, Twenteborg Hospital, Almelo, The Netherlands. Accepted for publication: May 16, 1997.

*Address for correspondence: Twenteborg Hospital, PO Box 7600, 7600 SZ Almelo, The Netherlands.

Present address:

‡Academic Hospital University of Amsterdam, Department of Anaesthesia, Academic Medical Centre, PO Box 22700, 1100 DE Amsterdam, The Netherlands.

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Ethics Committee and each patient gave informed consent to participate in the study. There were no exclusion criteria for age, ASA status or type of operation. Patients who required postoperative mechanical ventilation were excluded from the study. Institutional guidelines for anaesthetic and post-anaesthetic care did not change during the study. No bedside observer was present to verify the validity of the plethysmographic signal or to record the actions by the recovery room nurse.

PULSE OXIMETRY MONITORING

At the beginning of each day the LAL of each pulse oximeter (Criticare 504, Criticare Systems, Inc., Waukesha, WI, USA) was set randomly at either 90% (group 90) or 85% (group 85). The averaging epoch of each pulse oximeter was set at 3 s. A minimum value of the signal is required by the pulse oximeter to calculate Sp_{O_2} or else a loss of signal message is displayed. The display of this device shows the plethysmographic waveform, Sp_{O_2}, heart rate and alarm limits. A loud continuous audible alarm sounds when Sp_{O_2} decreases to or below the level of the LAL. It is possible to temporarily disable the alarm sound for a maximum of 2 min. Patients arriving from the operating room were allocated to the next available bed. Monitoring started immediately after arrival of the patient in the recovery room and was continued until the time of discharge. The sensor of the pulse oximeter was applied to a finger of the hand opposite to the arterial pressure cuff. Supplementary oxygen was administered by a nasal cannula to all patients during the initial postoperative period.

ANALYSIS OF ALARMS, ARTEFACTS AND HYPOXAEMIA

Heart rate, Sp_{O_2} and alarm status, together with time of day, were stored every 5 s in the memory of the pulse oximeter and transferred at the end of the day to a personal computer. Data for the first and last 3 min of monitoring were excluded to eliminate artefacts resulting from positioning and removal of the probe.

Episodes with Sp_{O_2} $\leqslant$90% were classified as hypoxaemia or artefact. An episode was classified as artefact if one or more of the following criteria were met:

—transient outlier: a single datum point (5 s resolution) differing by more than 4% from the surrounding data;

—loss of signal (as indicated by the pulse oximeter) occurring either 0–20 s before or 0–20 s after the episode of low Sp_{O_2};

—a step change in Sp_{O_2} of more than 10% in 5 s; and

—in an attempt to increase further the detection of artefacts, all other episodes with Sp_{O_2} $\leqslant$90% were inspected visually by the author (A. T. R-L., blinded for the group from which the data originated). If there was simultaneous jitter of Sp_{O_2} and heart rate, a movement artefact was suspected and data were classified as artefact.

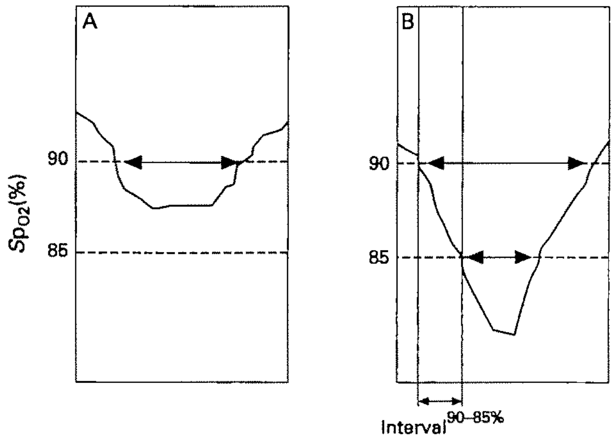

Figure 1 Examples of triggering of the alarm by low Sp_{O_2} values for two alarm limits (90% and 85%). In example A the episode triggers the alarm if the limit is set at 90%, but the episode resolves without having triggered the alarm if the limit is set at 85%. In example B the episode triggers the alarm with either limit, but the alarm is delayed if the limit has been set at 85%. Interval$^{90-85\%}$ denotes the time difference between Sp_{O_2} crossing the 90% threshold and the 85% threshold.

The number of episodes of hypoxaemia for the two thresholds (Sp_{O_2} $\leqslant$90% and $\leqslant$85%) was counted. Episodes where Sp_{O_2} decreased to values $\leqslant$90% were differentiated from those in which Sp_{O_2} remained above 85% (see example A in fig. 1) and from those where it decreased to less than 85% (example B in fig. 1). The time difference between Sp_{O_2} crossing the 90% threshold and the 85% threshold (interval$^{90-85\%}$) was calculated (example B in fig. 1).

The incidence of hypoxaemia (proportion of patients with at least one episode of hypoxaemia lasting $\geqslant$1 min) for three thresholds (Sp_{O_2} $\leqslant$90%, $\leqslant$85% and $\leqslant$80%) was determined. For each patient the cumulative duration of hypoxaemia (only episodes $\geqslant$1 min) for each of the thresholds was calculated.

Alarms were classified as either true positive (generated by hypoxaemia) or false positive (generated by artefact). In group 90 the effect on the number of alarms of introducing various theoretical delays (0–60 s, 5-s steps) between the onset of the alarm condition and triggering of the alarm was calculated.

Data are presented as counts and percentiles. Differences between the two groups were analysed using chi-square and Mann–Whitney tests. $P<0.05$ was considered significant. In group 85 the incidence of hypoxaemia was also expressed as relative risk (RR) compared with group 90. The confidence interval (CI) for relative risk was calculated with the Mantel–Haenszel chi-square statistic.

Results

During the 1-month period, we studied 647 patients; 320 patients were allocated to group 90 and 327 patients to group 85. Table 1 presents descriptive data for patients, anaesthesia and post-anaesthetic care. There were no differences between groups in

Table 1 Data on patients, anaesthesia and post-anaesthetic care. Data are counts or median (10–90th percentiles). Group 90=lower alarm limit of the pulse oximeter set at 90%, group 85=lower alarm limit of the pulse oximeter set at 85%

	Group 90 (*n*=320)	Group 85 (*n*=327)
Age (yr)	42 (21–73)	40 (21–75)
Sex (M/F) (*n*)	158/162	160/167
ASA I or II (*n*)	289	298
ASA III or IV (*n*)	31	29
General anaesthesia (*n*)	279	288
Regional anaesthesia (*n*)	41	39
Median duration of anaesthesia (min)	41 (11–93)	41 (10–91)
Median duration of monitoring in the recovery room (min)	44 (19–105)	44 (19–112)

Table 2 Incidence of hypoxaemia for three thresholds ($Sp_{O_2}\leq 90\%$, $Sp_{O_2}\leq 85\%$, $Sp_{O_2}\leq 80\%$). No.=absolute number of patients with at least one episode of hypoxaemia (artefacts excluded) lasting ≥1 min. Group 90=lower alarm limit of the pulse oximeter set at 90%; group 85=lower alarm limit of the pulse oximeter set at 85%; Sp_{O_2}=oxyhaemoglobin saturation; RR=relative risk, incidence of hypoxaemia in groups 85 divided by the incidence in group 90; CI=95% confidence interval for relative risk

	Group 90 (*n*=320)	Group 85 (*n*=327)		
Criteria for hypoxaemia	No. (%)	No. (%)	RR (CI)	*P*
$Sp_{O_2}\leq 90\%$	34 (11)	64 (20)	1.84 (1.26–2.69)	0.001
$Sp_{O_2}\leq 85\%$	6 (2)	19 (6)	3.10 (1.32–7.28)	0.009
$Sp_{O_2}\leq 80\%$	1 (0.3)	6 (2)	6.13 (0.92–37.5)	0.06

age, ASA status, duration of anaesthesia or post-anaesthetic care.

The incidence of hypoxaemia was greater in group 85 (table 2). Episodes of hypoxaemia ≤90% lasting for more than 1 min were present in 11% of patients in group 90 and in 20% of the patients in group 85 ($P<0.01$). Hypoxaemia ≤85% occurred in 2% of patients in group 90 and in 6% in group 85 ($P<0.01$). Hypoxaemia ≤80% occurred in 0.3% of patients in group 90 and in 2% in group 85 ($P=0.06$). The median cumulative duration of hypoxaemic episodes ≥1 min was not different between the groups (Sp_{O_2} ≤90%: 95 *vs* 175 s; Sp_{O_2} ≤85%: 165 *vs* 120 s).

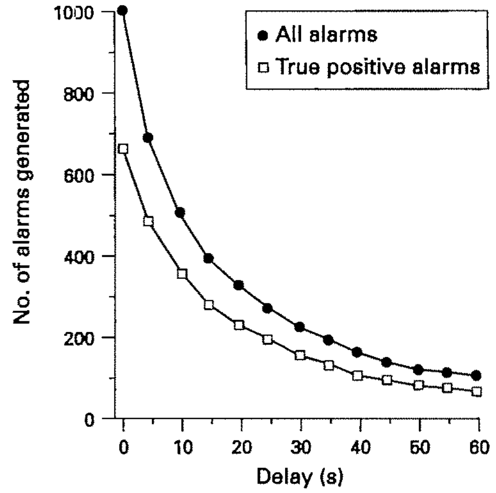

Figure 2 Number of alarms calculated that would have occurred when the lower alarm limit was set at 90% but a delay, which varies from 0 to 60 s, was introduced between the onset of pulse oximeter oxyhaemoglobin saturation below 90% and triggering of the alarm. The true positive alarms indicate hypoxaemia.

The number of episodes of desaturation ≤90% (without applying a criterion for the minimum duration of the episode) was 674 in group 90 and 938 in group 85. Sp_{O_2} decreased to or below 85% (see example B in fig. 1) in 104 desaturations in group 90 and in 197 desaturations in group 85. Table 3 shows the interval$^{90-85\%}$, the time required for oxyhaemoglobin saturation to decrease from 90% to 85%. The majority of desaturations less than 85% had an interval$^{90-85\%}$ less than 20 s in both groups. A longer interval$^{90-85\%}$ (≥20 s) occurred significantly more often in group 85 ($P<0.001$).

In group 90, 1007 alarms (674 true, 333 false) occurred, whereas in group 85, 395 alarms (285 true, 110 false) occurred. Figure 2 shows the number of alarms in group 90 that would have occurred with various delays from 0 to 60 s between the onset of the alarm condition (Sp_{O_2}=90%) and triggering of the alarm. As 60% of alarms lasted 15 s or less, introducing a 15-s delay in group 90 would reduce the number of alarms by the same amount as changing the LAL from 90% to 85% (group 90 with 15 s delay—398 alarms (71% true, 29% false) and group 85 with no delay—395 alarms (72% true, 28% false)).

Table 3 Time required for oxyhaemoglobin saturation to decrease from 90% to 85%. Group 90=lower alarm limit of the pulse oximeter set at 90%, group 85=lower alarm limit of the pulse oximeter set at 85%, Sp_{O_2}=oxyhaemoglobin saturation, interval$^{90-85\%}$=time difference between Sp_{O_2} crossing the 90% threshold and the 85% threshold

	No. of desaturations			
	Group 90		Group 85	
	$Sp_{O_2}\leq 85\%$ lasting less than 1 min	≤85% lasting more than 1 min	≤85% lasting less than 1 min	≤85% lasting more than 1 min
Interval$^{90-85\%}$				
0–15 s	70	5	89	13
20–55 s	17	0	33	15
≥1 min	8	4	35	12
Total No. of desaturations ≤85%	95	9	157	40

Discussion

Lowering the LAL from 90% to 85% is an effective means of reducing the number of audible alarms in the recovery room. However, with the LAL set at 85% the incidence of hypoxaemia lasting more than 1 min increased. Although the clinical relevance of this finding is unknown,[6] most clinicians would consider episodes of hypoxaemia of less than 85% lasting greater than 1 min potentially harmful. Therefore, based on the results of this study, setting the LAL at 85% cannot be recommended routinely.

Postoperative hypoxaemia has been implicated as a contributing factor for myocardial ischaemia, wound infection and cognitive dysfunction.[7–11] However, a large prospective study failed to demonstrate significant effects of pulse oximetry on outcome.[12 13] To increase the clinical relevance of a possible effect of the chosen LAL, we studied episodes with a minimum duration of at least 1 min. The six times higher incidence of severe hypoxaemia $\leqslant$80% in group 85 was not statistically significant (P=0.06). To exclude a type II error (a difference exists, but was not found in this study) a calculated group size of more than 2000 patients would be needed to achieve 80% power to detect a 50% reduction. This suggests that groups larger than the 320 patients we studied would have shown a statistically significant increased incidence of hypoxaemia $\leqslant$80% in group 85 also.

An alarm should initiate an intervention to reverse the ongoing desaturation. In addition, the underlying cause of the desaturation must be treated. In group 85 the majority of desaturations less than 90% resolved without triggering an alarm. However, the total number of these desaturations (in which the lowest Sp_{O_2} remained >85%, see example A in fig. 1) was 40% higher than in group 90. This suggests that the alarms resulted in therapeutic actions that corrected the underlying cause and prevented subsequent hypoxaemia.

In this study the speed of desaturation (as measured by the interval$^{90–85\%}$) was rapid in the majority of patients in both groups. When Sp_{O_2} decreases rapidly, changing the LAL from 90% to 85% delays the onset of the alarm only marginally. None the less, the incidence of desaturation less than 85% was higher in group 85. As can be seen in table 3 the speed of desaturation was more gradual in those patients who became hypoxaemic for more than 1 min in group 85. The interval$^{90–85\%}$ appears to be a crucial period in the institution of therapy to prevent prolonged hypoxaemia when desaturation is more gradual. This suggests that an early alarm is more effective in preventing longer and more severe desaturations than an alarm that sounds when Sp_{O_2} has decreased to less than 85%.

A high frequency of false alarms could be a legitimate argument to reduce the LAL with the aim of increasing specificity. Unfortunately, many technical problems (dislocation of the sensor, peripheral vasoconstriction, patient movement) produce artefactual rapid Sp_{O_2} decreases to values of 80–90%.[14] Previous studies have shown that as many as 50% of pulse oximeter alarms may be false.[3 4 15 16] In group 90 an average of one artefact per patient was present and 30% of the total number of alarms were false. We cannot exclude the possibility that, despite our artefact rejection algorithm and inspection of individual Sp_{O_2} data, several artefacts remained undetected. However, the majority of episodes with Sp_{O_2} $\leqslant$90% were transients which were excluded from calculations of hypoxaemia by the requirement of a minimum duration of 1 min. The criterion of longer than 1 min duration appears to be a valid cut-off point for the detection of true desaturation. Stausholm and colleagues found that 95% of low Sp_{O_2} episodes for more than 1 min were reflected in decreases of transcutaneous oxygen tension measurements.[17] Recent improvements in signal extraction technology may decrease the impact of motion artefact on the quality of the pulse oximeter signal and reduce the frequency of artefacts even further.[18 19] Monitors with a low frequency of false alarms should increase the acceptance by recovery personnel of a higher LAL setting.

Most manufacturers of pulse oximeters give the user the option to average several beats to prevent jitter of the display and unnecessary triggering of the alarm by transients. The benefit of averaging a larger number of beats is the reduction of random variability and diminished susceptibility to transients. As a consequence there is a temporal delay between actual and displayed Sp_{O_2} and delayed triggering of the alarm. Introducing a time delay between the detection of a low Sp_{O_2} and triggering of the audible alarm is an alternative way of reducing the frequency of alarms. Makivirta and Koski found that doubling the pre-alarm delay from 5 to 10 s reduced the mean alarm rate by 26%.[20] In our study a time delay of 15 s between the occurrence of the alarm condition and triggering of the audible alarm would have provided a similar reduction in the number of alarms as a decrease of the LAL from 90% to 85%. One advantage of introducing a time delay as opposed to lowering the LAL could be that hypoxaemia is detected earlier in patients whose Sp_{O_2} decreases more gradually. For example, in group 85, for 27 of the 40 desaturations ($\leqslant$85%, $\geqslant$1 min) the alarm would have been triggered earlier if an LAL of 90% and a 15 s delay of the alarm had been used. A second advantage might be improved attention to longer lasting episodes of mild hypoxaemia with Sp_{O_2} values of 85–90%. In contrast, an alarm delay might result in later detection of severe hypoxaemia if the rate of desaturation is very fast. Because the majority of desaturations had an interval$^{90–85\%}$ of less than 20 s, detection of hypoxaemia and institution of appropriate treatment would have been delayed by several seconds. This potential negative effect would have to balanced against the advantage of having a more specific alarm as a result of elimination of the majority of false alarms.

Uncertainty concerning the optimal LAL has to be acknowledged. To estimate the best cut-off point for a specific test a receiver operator characteristic curve (ROC) is often used.[21] This curve visualizes the trade-off between sensitivity and specificity. The sensitivity and specificity of individual Sp_{O_2} data points can be assessed (for example, by comparison with co-oximetry of arterial blood samples). However, it is impossible to calculate "sensitivity" or "specificity" for a postoperative pulse oximeter monitoring session. The number of false negative episodes (hypoxaemia present, no Sp_{O_2} alarm) is unknown and it is illogical to count the number of true negative episodes (no hypoxaemia, no alarm) because, by definition, each alarm is preceded by a true negative episode. The only variable that we could calculate with some confidence (based on the rejection algorithm) was the positive predictive value (number of true alarms divided by the total number of alarms). The positive predictive value was approximately 70% in both groups although the frequency of alarms was three-fold higher in group 90. Therefore, this value cannot be used to determine the optimal LAL.

In conclusion, the results suggest that recovery room personnel rely on Sp_{O_2} alarms to identify and treat hypoxaemia rather than observation of the patient and the pulse oximeter Sp_{O_2} display. Decreasing the alarm limit in an attempt to reduce frequent false alarms may lead to an increase in clinically relevant hypoxaemia. Maintaining the LAL at 90% and instituting a 15 s time delay before triggering the audible alarm is an equally effective approach to reduce the frequency of alarms that might not hamper rapid detection of hypoxaemia.

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Does nitrous oxide antagonize sevoflurane-induced hypnosis?

T. KATOH, K. IKEDA AND H. BITO

Summary

We have studied 64 ASA I and II patients (aged 20–60 yr) to determine if nitrous oxide affects sevoflurane requirements for achieving 50% probability of no movement in response to verbal commands (MAC$_{awake}$). Patients were allocated randomly to one of four nitrous oxide concentration groups (0, 20, 40 and 60 vol.%). Patients in each group received sevoflurane at two different end-tidal concentrations according to a predetermined randomization table. After steady state sevoflurane and nitrous oxide concentrations had been maintained for at least 15 min, patients were assessed as being awake or asleep. The MAC$_{awake}$ for sevoflurane was 0.63% and this was reduced significantly in a non-linear manner by increasing nitrous oxide concentration. A 50% reduction in MAC$_{awake}$ was produced by a nitrous oxide concentration of 45%. The reduction in MAC$_{awake}$ by nitrous oxide was non-linear; the interaction coefficient between nitrous oxide and sevoflurane being significantly less than zero (P=0.0238), indicating that the reduction in MAC$_{awake}$ by nitrous oxide was smaller than would be expected from simple additivity and that nitrous oxide antagonized the effects of sevoflurane in preventing response to verbal commands. (*Br. J. Anaesth.* 1997; **79**: 465–468).

Key words

Anaesthetics volatile, sevoflurane. Anaesthetics gases, nitrous oxide. Potency, anaesthetic, MAC.

End-tidal anaesthetic concentration at the first response to command and the concentration just preventing the response is defined as MAC$_{awake}$.[1] In some studies,[2 3] MAC$_{awake}$ values for isoflurane and sevoflurane were reported to be approximately one-third of MAC values, being different from those of halothane.[4] These MAC$_{awake}$ values were determined when anaesthetics were administered in combination and no other inhaled anaesthetic was used. Nitrous oxide is frequently combined with inhalation anaesthetics and its MAC$_{awake}$ value has been reported to be 0.64 MAC.[5] The drug interaction between nitrous oxide and volatile anaesthetic on awakening concentration is not known well, while nitrous oxide reduced halothane, enflurane, isoflurane and sevoflurane MAC values in a linear manner when added to each respective anaesthetic.[6–9] The purpose of this study was to determine the drug interaction between nitrous oxide and sevoflurane with regard to MAC$_{awake}$ values. We determined which, if any, of three different nitrous oxide concentrations (20, 40 and 60 vol.%) changed the MAC$_{awake}$ value in adult patients. Using the sevoflurane MAC$_{awake}$ determinations in the presence of nitrous oxide, the relationship between nitrous oxide and these volatile anaesthetic MAC$_{awake}$ fractions was determined.

Patients and methods

After obtaining approval from the departmental Ethics Committee and informed consent, we studied 64 patients of both sexes, ASA I and II, aged 20–60 yr, who were undergoing elective surgery. Exclusion criteria were a history of cardiac, pulmonary or renal disease; history of hearing disturbance or ear disease; history of oesophageal reflux or hiatus hernia; drug or alcohol abuse, or significant obesity (body mass index >30); and contraindications to inhalation induction. Patients were fasted for at least 8 h before surgery, were monitored in a routine manner and received no premedication.

The 64 patients were allocated randomly to one of four groups. Patients in group 1 received no nitrous oxide, while those in groups 2, 3 and 4 received end-tidal concentrations of 20, 40 and 60 vol.%, respectively. End-tidal sevoflurane concentrations were chosen to provide both adequate and inadequate anaesthesia at each nitrous oxide concentration, and were based on data from our previous MAC$_{awake}$ studies,[2 3] and the study of Dwyer and colleagues.[5] All patients received sevoflurane at two different concentrations. The inspired concentration of sevoflurane was adjusted to maintain the measured end-tidal concentration constant at the value predetermined according to a randomization scheme (fig. 1).

After an anaesthesia face mask was placed on the face of patients using a head strap, we confirmed that air leak from the margin of the mask was minimal when positive or negative airway pressure was applied to the inside of the mask. The mandible was displaced upward gently with two hands to avoid the

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TAKASUMI KATOH, MD, KAZUYUKI IKEDA, MD, FRCA, HIROMICHI BITO, MD, Department of Anaesthesiology and Intensive Care Medicine, Hamamatsu University School of Medicine, 3600 Handa-cho, Hamamatsu, 431-31 Japan. Accepted for publication: May 23, 1997.

Correspondence to T. K.

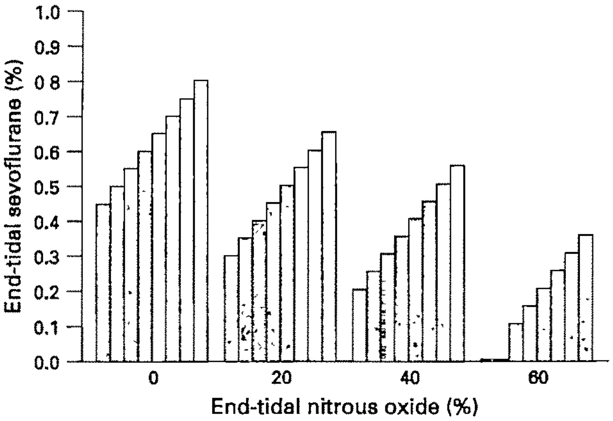

Figure 1 Assessment of loss of response to verbal command: end-tidal sevoflurane concentrations for each patient in each of the nitrous oxide concentration groups. Each bar represents four patients.

upper airway obstruction that may occur in unconscious patients. All patients breathed through the mask connected to a semi-closed anaesthetic system. To prevent contamination of end-tidal samples with inspired gas, the deadspace was augmented at the sampling port. Gas was withdrawn continuously from the sampling port, located between the face mask and deadspace, at a rate of 200 ml min^{-1}. Concentrations of nitrous oxide, carbon dioxide, sevoflurane and oxygen were measured continuously using an infrared anaesthetic gas analyser (Capnomac Ultima, Helsinki, Finland) which was calibrated before anaesthesia for each patient using a standard gas mixture. Patients breathed spontaneously, and ventilation was assisted if tidal volume was too small to provide adequate end-tidal sampling for measurement of anaesthetic concentration. Staff in the operating theatre were instructed to be quiet and not to physically stimulate the patient. Patients were instructed not to open their eyes, talk or move before a verbal command.

After steady state nitrous oxide and sevoflurane concentrations had been maintained for at least 15 min, patients were assessed as being awake or asleep by having their name called out in a normal tone and by being instructed to open their eyes. The patient's response to the verbal command was recorded as positive or negative, with slight movement of the eyelids considered a negative response.

STATISTICAL ANALYSIS

The $\text{MAC}_{\text{awake}}$ of sevoflurane and its reduction by nitrous oxide was evaluated using the following multiple independent variable logistic regression model:

$$P\,(\text{no response}) = \frac{1}{1+e^{-Z}}$$

$$Z = \beta_0 + \beta_1 X_1 + \beta_2 X_2 + \beta_{12} X_1 X_2$$

where X_1=end-tidal sevoflurane concentration, X_2=end-tidal nitrous oxide concentration, β_0=regression intercept constant, β_1=coefficient for sevoflurane, β_2=coefficient for nitrous oxide and β_{12}=coefficient for the product of the end-tidal sevoflurane and nitrous oxide concentrations (interaction coefficient). The likelihood ratio test was applied to determine the independent variables to be removed from the model. The $\text{MAC}_{\text{awake}}$ for a given end-tidal nitrous oxide concentration was determined by setting the probability of no response to 0.5 and solving for sevoflurane concentration as a function of end-tidal nitrous oxide concentration as follows:

$$X_1 = \frac{-(\beta_0 + \beta_2 X_2)}{\beta_1 + \beta_{12} X_2} \qquad (1)$$

The concentration of sevoflurane required to prevent response in 95% of patients ($\text{MAC}_{\text{awake95}}$) was also determined from each model by setting the probability of no movement to 0.95 and solving for sevoflurane concentration. The responses of patients to verbal command at each nitrous oxide concentration were subjected to probit analysis, in order to determine $\text{MAC}_{\text{awake}}$ and its 95% confidence limits. These statistical analysis was performed using SPSS software (SPSS, Inc., Chicago, IL, USA).

Results

Although a total of 64 patients were enrolled in the study, we could not assess eight responses in six patients because of pronounced excitatory phenomena and vomiting. Thus the results for 120 assessments in 58 patients are presented. This group included 27 men and 31 women with a mean age of

Table 1 Coefficient estimates for the logistic regression model. Nitrous oxide=end-tidal nitrous oxide concentration, sevoflurane=end-tidal sevoflurane concentration, interaction=product of nitrous oxide and sevoflurane, constant=regression intercept constant

Variable	Coefficient	SEM	*P*
Nitrous oxide	0.1677	0.0372	<0.0001
Sevoflurane	16.653	3.4364	<0.0001
Interaction	−0.135	0.0596	0.0238
Constant	−11.06	2.1814	<0.0001

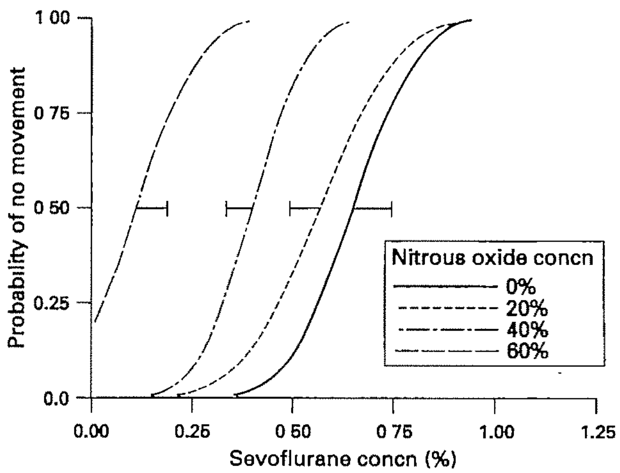

Figure 2 Probability of no movement in response to verbal command during sevoflurane-induced hypnosis in combination with 0, 20, 40 or 60% nitrous oxide. Error bars in the *X*-direction represent the 95% confidence limits around the $\text{MAC}_{\text{awake}}$ value.

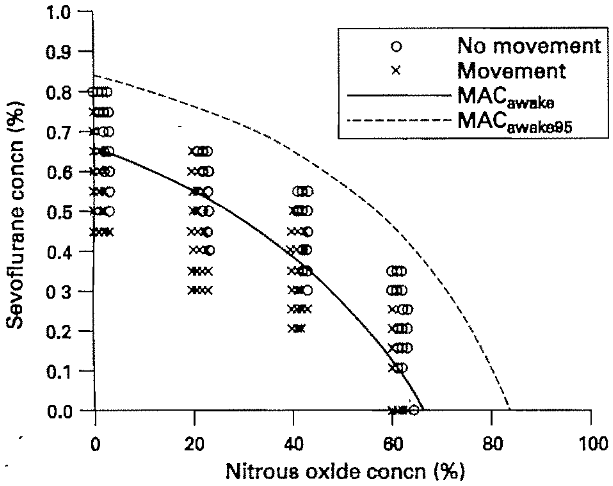

Figure 3 Reduction of sevoflurane concentration, by increasing concentrations of nitrous oxide, at which 50% (MAC$_{awake}$) or 95% (MAC$_{awake95}$) of patients did not respond to verbal commands.

47.5 yr (range 20–60 yr) and a mean body weight of 54.2 kg (40–81 kg).

The logistic model was fitted to 120 data sets of observed responses, end-tidal sevoflurane concentrations and end-tidal nitrous oxide concentrations. Coefficient estimates for the logistic regression model are presented in table 1. None of the three independent variables was removed from the model based on the likelihood ratio test. The interaction coefficient β_{12} was significantly less than zero (P=0.0238). The MAC$_{awake}$ and MAC$_{awake95}$ of sevoflurane in the absence of nitrous oxide were 0.63 and 0.93%, respectively. The probability of no movement in response to verbal command *vs* end-tidal sevoflurane concentration in the absence or presence of nitrous oxide is presented in figure 2. Reduction in the MAC$_{awake}$ of sevoflurane by nitrous oxide is presented in figure 3. MAC$_{awake}$ of nitrous oxide calculated as nitrous oxide concentration which would reduce MAC$_{awake}$ of sevoflurane to 0%, was 66%. A 50% reduction in MAC$_{awake}$ of sevoflurane was produced by a nitrous oxide concentration of 45%.

Discussion

The effect of nitrous oxide on the MAC$_{awake}$ value of sevoflurane has not been documented previously. Nitrous oxide, however, has been shown to reduce the MAC$_{awake}$ for isoflurane in a dose-dependent manner, with the MAC$_{awake}$ reported as 67%.[4] Thus 20, 40 and 60% nitrous oxide should correspond to MAC$_{awake}$ fractions of 0.3, 0.6 and 0.9, respectively. Chortkoff, Bennett and Eger examined the ED$_{50}$ for suppression of learning and ability to respond appropriately to verbal commands using the combination of isoflurane with 40% nitrous oxide. For both ED$_{50}$ values, a slightly higher value was reported than predicted by the assumption of additivity.[10] This indicates that the two anaesthetics are antagonistic with regard to this hypnotic effect. We found that nitrous oxide reduced the MAC$_{awake}$ of sevoflurane in a dose-related manner. The interaction coefficient between sevoflurane and nitrous oxide was significantly less than zero, indicating that nitrous oxide had a non-linear effect on reducing sevoflurane requirements and that sevoflurane requirements were greater than would be expected from simple additivity.

The results of this study showed that 33% nitrous oxide would reduce the MAC$_{awake}$ of sevoflurane to 68.1%, and that the sevoflurane MAC$_{awake}$ value is 18% greater than the value expected from simple additivity of the two agents. These findings correspond to those reported with isoflurane.[10] Nitrous oxide appears to antagonize the effect of sevoflurane to prevent responses to verbal commands. Nitrous oxide has some characteristics of a central nervous system stimulant.[11–13] It fails to supplement isoflurane-induced depression of cerebral metabolic rate[14] and may antagonize the electroencephalographic effects of volatile agents.[15] A study by Yli-Hankala and colleagues showed that the addition of nitrous oxide to isoflurane decreased the frequency and duration of isoflurane-induced burst suppressions in the electroencephalogram in an apparently non-additive interaction.[16] Although we did not monitor the EEG in this study, this activating mechanism may explain our findings.

We reported that nitrous oxide produced a non-liner reduction in thiopentone requirements for preventing response to verbal commands.[17] The findings of this study agree with those of our previous study. The observed deviation from linearity of the interaction between nitrous oxide and sevoflurane was rather small, so that clinical relevance may be questioned.

It has been shown that the interaction between nitrous oxide and volatile agents such as halothane, enflurane or isoflurane is additive in the sense that the linear combination of two MAC fractions of nitrous oxide and the volatile agent equating to 1.0 MAC also prevents response to skin incision in 50% of patients. We reported that the MAC of sevoflurane was also reduced by nitrous oxide in an additive manner.[9] Recent studies by Cole and colleagues claimed to have shown a non-linear contribution to the interaction of nitrous oxide with halothane, enflurane and isoflurane in rats.[18 19] Gauman, Mustaki and Tassonyi demonstrated that ratios of MAC$_{awake}$ to MAC differed for the anaesthetics halothane, enflurane and isoflurane in humans.[4] Their findings do not support a unitary mechanism of anaesthetic action. Instead, response to noxious stimuli such as skin incision and response to verbal command seem to be depressed by different mechanisms. Although nitrous oxide has an additive effect with these volatile agents in preventing movement in response to surgical incision, this may not translate to additivity for suppression of responsiveness to a verbal command.

In our study we demonstrated that nitrous oxide had a non-linear effect on reducing sevoflurane, and the shape of the reduction curves in MAC$_{awake}$ by nitrous oxide differed from that in MAC. In rats, acute decerebration (removal of part of the central nervous system—cortex and thalamus) did not affect the concentration of isoflurane required to prevent movement in response to tail-clamping.[20] In goats with the brain preferentially anaesthetized, higher anaesthetic concentrations were required to prevent movement in response to a clamp; this supports the importance of subcortical structures, such as the spinal cord, in the generation of purposeful movement in response to a painful stimulus under general anaesthesia.[21] These observations suggest that motor responses in response to a noxious stimulus may be mediated primarily by subcortical structures, including the spinal cord, at least in lower animals. In contrast, purposeful responsiveness to a verbal command apparently requires intact cortex function. Different end-points (no response to verbal command *vs* no response to noxious stimulus) may be associated with different sites of anaesthetic action.[22] Therefore, the type and degree of interaction between any two anaesthetics may depend on the clinical end-point used.

We calculated the $\text{MAC}_{\text{awake}}$ of nitrous oxide as the concentration of nitrous oxide which would reduce the $\text{MAC}_{\text{awake}}$ of sevoflurane to 0% by extrapolating equation (1). The predicted $\text{MAC}_{\text{awake}}$ value (66%) was almost equal to that determined by Dwyer and colleagues.[5] Nitrous oxide alone did not reliably prevent conscious awareness during anaesthesia. The probability of no movement in response to verbal command *vs* end-tidal sevoflurane concentration in the presence of 60% nitrous oxide revealed that nitrous oxide would prevent 20% of patients from responding to verbal commands at this nitrous oxide concentration in the absence of sevoflurane (fig. 2). Dwyer and colleagues reported that the percentage of volunteers not responding purposefully to verbal commands at 0.6 MAC (62%) of nitrous oxide was 20%.[5]

In conclusion, we have studied the interaction between nitrous oxide and sevoflurane on loss of consciousness. The $\text{MAC}_{\text{awake}}$ of sevoflurane was 0.63% and this was reduced significantly in a non-linear manner by increasing nitrous oxide concentration. A 50% reduction in the $\text{MAC}_{\text{awake}}$ value was produced by a nitrous oxide concentration of 45%. The reduction in $\text{MAC}_{\text{awake}}$ by nitrous oxide was less than would be expected from simple additivity at low concentrations.

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Effect of incremental doses of sevoflurane on cerebral pressure autoregulation in humans

S. GUPTA, K. HEATH AND B. F. MATTA

Summary

We have examined cerebral pressure autoregulation while awake, and during 0.5 and 1.5 MAC of sevoflurane anaesthesia in 10 patients undergoing non-intracranial neurosurgical procedures. All patients received a standardized anaesthetic comprising premedication with temazepam 20 mg orally, a sleep dose of propofol, fentanyl 1 μg kg^{-1} and vecuronium 0.1 mg kg^{-1}. After tracheal intubation, the lungs were ventilated with a mixture of air and oxygen to mild hypocapnia. Routine monitors included ECG, continuous and intermittent non-invasive arterial pressure, pulse oximetry and end-tidal capnography. In addition, blood flow velocity (vmca) was measured by insonating the middle cerebral artery transtemporally using a 2-MHz transcranial Doppler probe. Cerebral pressure autoregulation was tested by increasing mean arterial pressure (MAP) by approximately 20 mm Hg using an infusion of phenylephrine and simultaneously recording vmca. The index of autoregulation (IOR) during each period of the study, calculated as the ratio of percentage change in estimated cerebral vascular resistance (CVRe=MAP/vmca) to percentage change in MAP, was compared using ANOVA. vmca during 0.5 and 1.5 MAC of sevoflurane anaesthesia was significantly lower than that while awake (mean 79 (SD 24), 54 (15) and 51 (12) cm s^{-1}, respectively; $P<0.05$). There was no significant change in vmca with the increase in MAP while awake, or during 0.5 or 1.5 MAC of sevoflurane anaesthesia and IOR was similar under the three conditions (0.82 (0.11), 0.83 (0.04) and 1.0 (0.03), respectively). We conclude that cerebral pressure autoregulation remained intact during sevoflurane anaesthesia in humans. (*Br. J. Anaesth.* 1997; **79**: 469–472).

Key words
Anaesthetics volatile, sevoflurane. Brain, blood flow. Measurement techniques, Doppler ultrasonography.

Cerebral pressure autoregulation, a sensitive mechanism impaired in a dose-dependent manner by inhaled anaesthetics, minimizes changes in cerebral blood flow (CBF) when cerebral perfusion pressure changes.[1–4] This study was designed to investigate the effects of incremental doses of the recently introduced inhalation anaesthetic, sevoflurane, on cerebral pressure autoregulation in humans.

Patients and methods

After obtaining local Ethics Committee approval and written informed consent, we studied 10 ASA I or II patients, aged 25–66 yr (mean 48 yr), weighing 52–90 kg (mean 72 kg), undergoing non-intracranial neurosurgical procedures. Patients with neurological, respiratory or cardiovascular disease and those receiving psychotropic drugs were excluded. Patients less than 18 yr of age were also excluded. Routine monitors included ECG, continuous and intermittent non-invasive arterial pressure (Finapress and Dinamap, Ohmeda, USA), pulse oximetry and capnography. In addition, a 2-MHz transcranial Doppler ultrasound probe (DWL Multidop, Sipplingen, Germany) was used to measure the time-averaged mean flow velocity (*v*mca) in the middle cerebral artery (MCA). The probe was secured in position in a specially designed frame after using standard criteria to obtain the best signal possible from the vessel at a depth of 45–55 mm.[5] All patients received a standard anaesthetic comprising premedication with temazepam 20 mg orally, propofol 2–2.5 mg kg^{-1}, fentanyl 1 μg kg^{-1} and vecuronium 0.1 mg kg^{-1}, and their lungs were ventilated with a mixture of air and oxygen ($F_{I_{O_2}}$ 0.35) to maintain mild hypocapnia. Body temperature was maintained greater than 36 °C in all patients using warmed i.v. fluids and a warming blanket. Repeated doses of vecuronium were used to maintain neuromuscular block as required. When necessary, an infusion of phenylephrine was used to maintain mean MAP as close as possible to baseline.

AUTOREGULATION TESTING

Cerebral pressure autoregulation was examined three times in each patient: while awake, during 0.5 and 1.5 MAC of sevoflurane anaesthesia (after

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SANJEEVA GUPTA, FRCA, KAREN HEATH, FRCA, BASIL F, MATTA, FRCA, Department of Anaesthesia, Addenbrooke's Hospital, Box 93, Hills Road, Cambridge CB2 2QQ. Accepted for publication. May 22, 1997.

Correspondence to B. F. M.

Table 1 Mean (SD) data during pressure autoregulation testing. *$P<0.05$ compared with awake; †$P<0.05$ compared with baseline (ANOVA)

	Awake	0.5 MAC sevoflurane	1.5 MAC sevoflurane
End-tidal CO_2 (kPa)	5.1 (0.6)	4.5 (0.6)	4.5 (0.5)
Baseline *v*mca (cm s^{-1})	79 (24)	54 (15)*	51 (12)*
Autoregulation *v*mca (cm s^{-1})	82 (23)	56 (11)*	51 (12)*
Baseline heart rate (beat min^{-1})	81 (15)	77 (15)	63 (12)
Autoregulation heart rate (beat min^{-1})	60 (12)†	65 (15)†	52 (7)†
Baseline MAP (mm Hg)	95 (10)	86 (12)	85 (13)
Autoregulation MAP (mm Hg)	117 (10)†	109 (14)†	106 (15)†
Change in MAP (mm Hg)	22 (6)	23 (4)	22 (3)
IOR	0.82 (0.11)	0.83 (0.04)	1.0 (0.03)

15 min of unchanged end-tidal concentration and before the start of surgery). Autoregulation was tested by inducing an increase in MAP of approximately 20 mm Hg using an infusion of 0.01% phenylephrine and simultaneously recording *v*mca. *v*mca and MAP were used for subsequent calculation of the estimated cerebral vascular resistance (CVRe=MAP/*v*mca) at each stage.

The index of autoregulation (IOR), defined as the ratio of percentage change in estimated CVRe to percentage change in MAP, was calculated for each period of the study.[6] Theoretically, no change in *v*mca should occur if the percentage change in CVRe is equal to the percentage change in MAP. Thus an IOR of 1 implies perfect autoregulation and an IOR of 0, complete disruption of autoregulation. Based on previously published autoregulation data in humans, we considered a change less than 15% in IOR to be clinically insignificant.[7] Power analysis showed that for a power of 0.8, an alpha error of 0.05 and a beta error of 0.20, the required number of patients to reject the null hypothesis was 10. The computed IOR, and data recorded before and after the phenylephrine-induced increase in MAP, were analysed using ANOVA. $P<0.05$ was considered significant.

Results

The major findings of the study are shown in table 1. There was no significant change in patient body temperature, arterial saturation or end-tidal carbon dioxide. Mean *v*mca was significantly lower during 0.5 and 1.5 MAC of sevoflurane anaesthesia (79 (SD 24), 54 (15) and 51 (12) cm s^{-1}, respectively) ($P<0.05$).

Baseline MAP, heart rate and the phenylephrine-induced increase in MAP were similar during the three periods of the study. The phenylephrine-induced increase in MAP did not cause a significant change in *v*mca while awake, or at 0.5 or 1.5 MAC of sevoflurane anaesthesia. Hence, the calculated IOR values were similar during the three periods of the study (0.82 (0.11), 0.83 (0.04) and 1.0 (0.03), respectively).

Discussion

We have shown that sevoflurane did not affect cerebral pressure autoregulation in humans. This is in contrast with other commonly used inhalation agents which abolish autoregulation in a dose-dependent manner.[3] Therefore, a degree of healthy criticism is warranted in order to provide a reasonable explanation for our findings.

Carbon dioxide is a potent cerebral vasodilator. Hypercapnia exhausts the cerebral vasodilator response to changes in perfusion pressure thus reducing autoregulatory capacity.[8] In contrast, hypocapnia increases cerebral vascular tone resulting in improved cerebral autoregulation.[9] The end-tidal carbon dioxide concentration during the course of the study remained relatively unchanged at just less than 5 kPa and is unlikely to have significantly influenced the autoregulatory mechanism.

The other drugs used during the study do not have direct cerebrovascular effects. Propofol was used for induction of anaesthesia and most of the induction dose would have undergone re-distribution before autoregulation testing during sevoflurane anaesthesia was commenced. Fentanyl and vecuronium have no direct cerebral vasodilator effects and do not affect cerebral autoregulation.[10 11]

We used transcranial Doppler ultrasonography (TCD), a non-invasive inexpensive device, as a measure of CBF. Although TCD does not provide a direct measure of CBF, provided the angle of insonation and the diameter of the vessel insonated remain constant, changes in *v*mca accurately reflect relative changes in CBF.[12–14] We used a frame designed specially to maintain the probe in position, thus ensuring that the angle of insonation remained constant throughout the study. There is also now ample direct and indirect evidence to support the view that the diameter of the MCA does not change significantly with changes in arterial pressure, Pa_{CO_2} or the use of anaesthetic or vasoactive agents.[13–18]

As we measured *v*mca and not absolute CBF, we could only estimate cerebral vascular resistance (CVRe). We then calculated the index of autoregulation by dividing the percentage change in CVRe by the percentage change in MAP. This method has been used before as a measure of cerebral autoregulatory capacity.[3 6] As reported previously, an IOR of 1 indicates that the percentage change in CVRe is the same as the percentage change in MAP and no change in CBF results; perfect autoregulation. Complete absence of autoregulation gives an IOR of 0. The calculated IOR values during 0.5 and 1.5 MAC of sevoflurane anaesthesia were similar to awake values, indicating that cerebral autoregulation remained intact during sevoflurane anaesthesia in humans. Power analysis ensured that 10 patients were sufficient to reject the null hypothesis with a power of 0.80, an alpha error of 0.05 and a beta error of 0.20, assuming a change less than 15% in the IOR to be clinically insignificant.[7]

Although we examined autoregulation in only one direction (increase in pressure), we chose a level of MAP in the middle of the autoregulation curve. Therefore, there is no reason to assume that a decrease instead of an increase in MAP would have yielded different results. This has been confirmed recently by Tiecks and colleagues who found that the ability of the cerebral circulation to autoregulate was similar if MAP was increased or decreased.[19]

We chose to examine the effects of 0.5 and 1.5 MAC of sevoflurane on cerebral pressure autoregulation to allow comparison with published data on other inhalation agents. For example, both isoflurane and desflurane abolish autoregulation at 1.5 MAC.[3] Furthermore, it is unlikely that an inhalation agent may be used in neuroanaesthetic practice at concentrations greater than 1.5 MAC.

Our findings are in agreement with the recently published reports on cerebral autoregulation during sevoflurane anaesthesia. Hanel and colleagues have shown that cerebral pressure autoregulation is maintained during 0.5 and 2.0 MAC of sevoflurane anaesthesia in pigs.[20] Kitaguchi and colleagues demonstrated that cerebral pressure autoregulation is maintained during 0.88 MAC of sevoflurane anaesthesia in patients with ischaemic cerebrovascular disease undergoing extracranial intracranial bypass.[21] Cho and co-workers also reported that cerebral pressure autoregulation was maintained during 1.2 MAC of sevoflurane anaesthesia or a mixture of 1.2 MAC of sevoflurane with 60% nitrous oxide in six patients.[22] Why should sevoflurane, an agent similar to isoflurane in many of its systemic effects, have a significantly different effect on cerebral autoregulation?

It is generally accepted that the effect of inhalation anaesthetics on the cerebral vasculature is dependent on the balance between their direct cerebral vasodilator action and the indirect vasoconstrictive effect consequent upon normal flow–metabolism coupling.[23] Thus the net effect on CBF of adding an inhalation agent depends on the level of cerebral metabolism before the agent is added. When cerebral metabolism is already depressed, the agent increases CBF by vasodilatation of cerebral vessels. However, if the agent is administered to patients who are in a "light plane of anaesthesia" or awake, its cerebral metabolic depressant effect leads to a decrease in CBF. Hence, while at lower concentrations the major effect on CBF is vasoconstrictive secondary to flow–metabolism coupling, at higher concentrations the direct vasodilator effect predominates with increases in CBF and loss of cerebral autoregulation.[24] From recently published data and from work carried out at our institution, it would appear that sevoflurane has a less direct vasodilator effect than either isoflurane or desflurane.[25 26] Furthermore, work carried out in this institution suggests that the direct vasodilator effect of sevoflurane at 1.5 MAC is approximately 30% of the effect with isoflurane.[26] This explains maintenance of autoregulation at 1.5 MAC, as the major effect is vasoconstriction secondary to flow–metabolism coupling. Hence the cerebral vasculature remains capable of responding to changes in perfusion pressure. Indeed, *v*mca values at 0.5 and 1.5 MAC are in agreement with this hypothesis.

We conclude that cerebral pressure autoregulation was preserved during 0.5 and 1.5 MAC of sevoflurane anaesthesia in humans. This is advantageous for an agent that has many properties favouring its use in neuroanaesthetic practice.

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Comparison of isoflurane with propofol on respiratory cilia

J. H. RAPHAEL AND M. W. BUTT

Summary

We have investigated the effects of two techniques of clinical anaesthesia on human respiratory cilia by measuring cilia beat frequency of nasal tissue. In a randomized, controlled study, 13 patients undergoing either inhalation anaesthesia with isoflurane or total i.v. anaesthesia with propofol and alfentanil had nasal ciliated epithelial samples removed at the beginning and after 1 h of anaesthesia. Mean cilia beat frequency in the group anaesthetized with isoflurane changed significantly from 11.5 (95% confidence interval (CI) 10.7–12.2) Hz to 9.1 (8.1–10.1) Hz after anaesthesia whereas in the group anaesthetized with propofol and alfentanil there was a change from 11.5 (10.7–12.2) Hz to 11.0 (10.2–11.8) Hz (ns). The difference between the anaesthetic agents on cilia beat frequency was significant (MANOVA, $P<0.01$). These data suggest that different anaesthetic agents may impair respiratory defence mechanisms to differing extents. (*Br. J. Anaesth.* 1997; **79**: 473–475).

Key words

Lung, trachea. Lung, mucus. Anaesthetics i.v., propofol. Anaesthetics volatile, isoflurane.

Advances in anaesthesia over the past few decades have produced a very low level of mortality associated with anaesthesia; a recent report found that only three deaths out of almost 0.5 million procedures resulted from anaesthesia alone.[1] Consequently, greater attention has focused on morbidity associated with anaesthesia, especially on serious forms of morbidity. An important and common type of morbidity is that caused by pulmonary infection. Prospective studies have described an incidence of 6–21%.[2–5]

The causes of postoperative pulmonary infections are multifactorial but depend on clearance of lung secretions. This requires effective coughing and ciliary transport of respiratory mucus. Most attention has been directed at improving coughing after its impairment by the effects of both anaesthesia and surgery. However, although it has been known for some time that anaesthetic agents can impair mucus transport rates,[6 7] there have been few investigations.

It is most likely that impairment of mucus transport is caused by effects of the anaesthetic agents on the cilia.[8] The most important determinant of ciliary transport of mucus is ciliary beat frequency[9] and we have demonstrated previously, *in vitro*, differential effects of anaesthetic agents on cilia with a depressant effect after inhalation agents but no effect with propofol.[10 11] This raises the possibility of a difference in clinical practice between the two techniques of inhalation anaesthesia and total i.v. anaesthesia (TIVA).

To investigate this possibility further, we have conducted a double-blind, randomized, controlled study of the effects of these two anaesthetic techniques on human respiratory cilia beat frequency.

Patients and methods

After obtaining Ethics Committee approval and informed patient consent, we studied 13 patients (nine males, four females, aged 27–71 yr) undergoing elective peripheral body surgery under general anaesthesia. Anaesthesia was induced with fentanyl 50–125 μg and propofol 160–320 mg, and a sample of ciliated nasal epithelial cells was obtained by passing a bronchoscopy brush over the inferior nasal turbinates as described previously.[12] The brush was agitated in M199 medium to remove the cells.

Patients were allocated randomly to maintenance of anaesthesia with either an inhalation anaesthetic agent or TIVA as follows. Anaesthesia was maintained by face mask anaesthesia with 30–45% oxygen in air flowing via a circle system at 3 litre min^{-1} with the addition of either isoflurane or an i.v. infusion of propofol and alfentanil. Propofol and alfentanil were mixed together in a 60-ml syringe containing propofol 60 ml and alfentanil 2 mg. The concentration of isoflurane and the rate of propofol–alfentanil infusion were determined by clinical response to surgery. All patients received ketorolac 15 mg i.m. and local anaesthetic infiltration or regional nerve block of the surgical field before commencement of surgery.

The following variables were monitored and recorded: fractional inspired oxygen concentration, end-tidal carbon dioxide concentration, oesophageal temperature, non-invasive arterial pressure, ECG, arterial oxygen saturation and end-tidal isoflurane concentration.

J. H. RAPHAEL, MD, FRCA, M. W. BUTT, MB, BS, BA, FRCA, University Department of Anaesthesia, Leicester Royal Infirmary, Leicester LE1 5WW. Accepted for publication: May 28, 1997.

After 1 h of anaesthesia a second sample of nasal ciliated epithelium was obtained in the same manner as before.

Measurement of cilia beat frequency was undertaken as described and validated previously.[13] Within 5 min of removal from the patient, the ciliated samples were transferred to a heated chamber for viewing by differential interference contrast microscopy (Nikon Diaphot 200, Nikon UK). The image of the cilia was transmitted to a video monitor (Sony KX-14CPI) via a video camera (Panasonic vw-CL 1 1 0-AK) to provide a magnified image of the moving cilia of 3000×. A pinhead photodiode with a diameter of 1 mm^2 was attached to the monitoring screen to detect interference in light caused by the moving cilia. The voltage across the diode was amplified to provide a signal to an oscilloscope greater than 0.2 V and low pass filtered with a cut-off above 25 Hz. The changing voltage signals were sampled by an analogue-to-digital converter. The voltage signals were collected over a period of 15 s and divided into three sequential 5-s intervals for analysis. Data were analysed by software written in Mathematica 2.2 to provide a power spectrum using fast Fourier transforms. The peak of the power spectrum was taken to represent cilia beat frequency. Acceptable ciliated edges for measurement were defined as those devoid of mucus and at least 60 µm in length. Measurements were not taken from individual cells or disrupted edges. Eight areas of continuous ciliated epithelium were measured from each sample of ciliated tissue. The peaks of the power spectra were analysed by MANOVA applied to the differences between the treatment groups with significance taken at $P<0.05$.

Results

Six patients were allocated randomly to receive isoflurane and seven to receive TIVA. Patients underwent lower limb varicose vein operations or day-case limb orthopaedic procedures. The groups were similar in age, sex distribution, oxygen saturation, carbon dioxide tension and core temperature (table 1). The range of end-tidal isoflurane concentrations measured was 1.5–2.5% and the range of propofol delivered was 500–600 mg. Mean cilia beat frequency in the group anaesthetized with isoflurane changed from 11.5 (95% confidence interval (CI) 10.7–12.2) Hz to 9.1 (8.1–10.1) Hz after anaesthesia and in the group anaesthetized with propofol and alfentanil from 11.5 (10.7–12.2) Hz to 11.0 (10.2–11.8) Hz (fig. 1). The difference between the anaesthetic agents on cilia beat frequency was significant (MANOVA, $P<0.01$).

Table 1 Patient data and variables measured during anaesthesia (mean (95% CI)) in the group who received inhalation anaesthesia (IA) compared with the total i.v. anaesthesia (TIVA) group

	Group IA	Group TIVA
n	6	7
Sex (M/F)	4/2	5/2
Age (range) (yr)	29–38	27–71
End-tidal isoflurane concn (%)	1.5–2.5	—
Propofol delivered (mg)	—	500–600
$F_{I_{O_2}}$	0.35–0.40	0.36–0.45
$S_{p_{O_2}}$ (%)	96–98	96–98
End-tidal CO_2 (kPa)	4.5–6.8	5.0–7.0
Core temperature °C,		
30 min	34.9–36.8	35.4–36.8
60 min	34.7–36.5	35.1–36.5

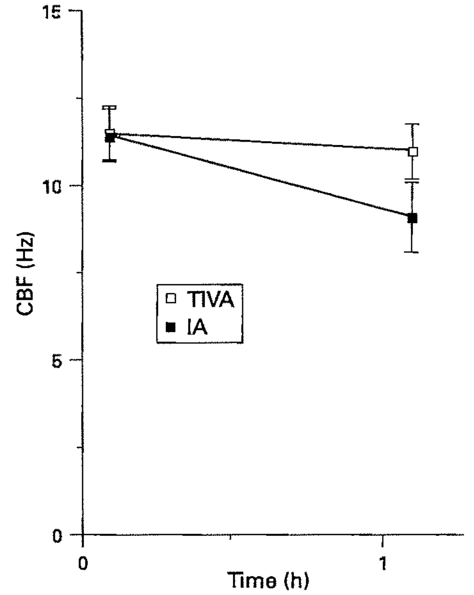

Figure 1 Effects of inhalation anaesthesia (IA) and total i.v. anaesthesia (TIVA) on human nasal cilia beat frequency (CBF) (mean (95% CI)).

Discussion

We have found a difference in the beat frequency of nasal cilia exposed to inhalation agent anaesthesia with isoflurane compared with TIVA with propofol and alfentanil.

The reduction in beat frequency after 1 h of isoflurane anaesthesia was 2.4 Hz. This reduction of more than 20% is significant in terms of its effects on mucus transport. This is based on the logarithmic relationship between cilia beat frequency and mucus transport rate[14] such that modest reductions in beat frequency of the cilia are accompanied by greater reductions in mucus transport rate, and represents approximately a 50% reduction in mucus transport rate.

In previous work we have shown that a bolus dose of propofol has no effect on nasal cilia beat frequency measured 1 h later[13] and in another investigation we showed there were no opioid receptors on the nasal cilia.[15] Therefore, a bolus of propofol and fentanyl would not be expected to have an effect on cilia beat frequency. Baseline cilia beat frequency was similar in the two groups and is in close agreement with that reported previously in awake volunteers.[16]

End-tidal isoflurane concentration were 1.5–2.5%. In our earlier *in vitro* experiments, we found similar reduction of 3 Hz with 2 MAC of isoflurane.[17] In an *in vitro* study of propofol on cilia beat frequency in which 70 µmol litre^{-1} (approximately twice the concentration during TIVA) was perfused over ciliated tissue, we found no change in cilia beat frequency.[11] Thus our *in vitro* investigations concur with the findings from this clinical study.

We undertook a comparative study of patients under anaesthesia because there were several limitations to our earlier *in vitro* investigations. It is likely that the concentrations of drugs in the cilia are different when drugs are delivered to tissue samples in the laboratory compared with delivery by anaesthetic equipment to patients. Indeed the difference between these two agents on the cilia may be the result of different methods of delivery in clinical practice, with gas phase drug delivery possibly being more harmful than delivery to the cilia via the bloodstream. Furthermore, previous *in vitro* work did not include a controlled investigation comparing these two agents.

Various methods have been described for measurement of cilia beat frequency but are limited to *in vitro* techniques. Laser light scattering spectroscopy is a recent and sophisticated light technique that is not restricted to *in vitro* use[18]; however, this technique is invasive and its use has been restricted by its expense which has limited its validation. The *in vitro* transmitted light technique is the most widely used and reliable technique for measurement of cilia beat frequency. It is reproducible, convenient and requires minimal subjective assessment; however, it is subject to the effects of extraneous vibrations and it cannot detect individual cilia. We have overcome the problem of vibration by setting the imaging system on an anti-vibration concrete base.[13] Using an *in vitro* method for determination of cilia beat frequency introduces possible effects on the cilia by removal from their natural environment; however, the experiment was conducted in a controlled manner to take account of this.

It has been demonstrated by other workers that cilia beat frequency measured from nasal brushings is the same as that from samples taken from further down the respiratory tract[19] and therefore nasal samples are likely to be representative of cilia from more distal parts of the lungs. Therefore, we elected to use nasal tissue for analysis as this is a less invasive sampling technique and modified the anaesthetic technique accordingly. By using a face mask, the inhalation anaesthetic agents passed over these ciliated cells in a similar manner to effects on bronchial cilia when using other airway devices.

The effects of a reduction in cilia beat frequency on respiratory defences and the subsequent development of pulmonary infections is not known. Retrospective comparisons of inhalation anaesthesia and TIVA have not demonstrated a difference in this regard.[20] A controlled prospective study is required including groups at risk of postoperative pulmonary infections to determine if the choice of anaesthetic technique is important in this regard.

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Platelet function is inhibited by nitric oxide liberation during nitroglycerin-induced hypotension anaesthesia

H. Aoki, M. Inoue, T. Mizobe, M. Harada, H. Imai and A. Kobayashi

Summary

The inhibitory effects of nitroglycerin (NTG) on platelet function and the mechanisms of inhibition have been studied *in vitro*, but not *in vivo*. Therefore, we have investigated the effects of NTG on platelet function in eight patients undergoing orthopaedic surgery. Simultaneous measurements of platelet aggregation and change in intracellular calcium concentrations were performed in Fura-2 loaded platelets using thrombin as a stimulator. Intraplatelet concentrations of cyclic 3′,5′-guanine monophosphate (cGMP) were measured by radioimmunoassay, and the concentration of nitrite ion was also measured. Continuous i.v. infusion of NTG 4–8 μg kg^{-1} min^{-1} significantly inhibited platelet aggregation and the increase in intracellular Ca^{2+} concentration (first phase, mean 439.9 (SEM 68.7) *vs* 210.6 (38.7) nmol litre^{-1}; second phase, 154.4 (19.8) *vs* 106.7 (18.0) nmol litre^{-1}). The concentration of cGMP (from 0.633 (0.098) to 1.764 (0.578) pmol/10^9 platelets) and the concentration of nitrite ion (from 532.6 (17.6) to 724.4 (34.8) nmol litre^{-1}) also increased significantly after infusion of NTG. The NTG concentration in plasma was of the order of 10^{-8} mol litre^{-1}. We have demonstrated that *in vivo*, NTG increased intraplatelet cGMP concentrations and inhibited platelet function; one mechanism of this effect is likely to be related to nitric oxide liberation from NTG bioconversion. (*Br. J. Anaesth.* 1997; **79**: 476–481).

Key words
Anaesthetic techniques, hypotensive. Pharmacology, nitroglycerin. Gases non-anaesthetic, nitric oxide. Blood, platelets. Blood, coagulation.

Organic nitrates, such as nitroglycerin (NTG), have been used widely for the treatment of myocardial infarction and angina pectoris.[1] It has been reported that the major pharmacological action of NTG is vasodilatation of vascular smooth muscle.[2] The effects of NTG on platelets may also represent an important pharmacological effect.[3] The inhibitory effects of NTG on platelet function were first demonstrated by Hampton and colleagues,[4] and have subsequently been reported by many investigators. Prevention of platelet aggregation by several organic nitrates may be effective both prophylactically and therapeutically.[5] However, in studies which demonstrated these effects of NTG *in vitro*, the concentrations used were higher than those pharmacologically attainable *in vivo*.[6–9] In fact, in one *in vivo* study infusion of NTG at approximately 1 μg kg^{-1} min^{-1} failed to demonstrate similar effects of NTG on platelet aggregation.[10] Much higher doses of NTG are given for induced hypotensive anaesthetic techniques during surgery, thus providing an opportunity to study the effects of NTG on platelet function *in vivo* at doses higher than those reported previously.

Patients and methods

This study was approved by our Institutional Committee on Human Research, and informed consent was obtained from all subjects. We studied eight patients (four men and four women) undergoing orthopaedic surgery of the hip joint. Mean age was 50.9 (range 22–75) yr. All patients were ASA I or II, and none had any known haematological abnormalities. Patients being treated with medications that may affect platelet function were excluded.

Patients were premedicated with atropine 0.01 mg kg^{-1} and hydroxyzine 1 mg kg^{-1} i.m. Thirty minutes later, thiopentone 5 mg kg^{-1} was administered i.v. for induction of general anaesthesia, and tracheal intubation was facilitated with vecuronium. Thereafter, anaesthesia was maintained with isoflurane and 66% nitrous oxide in oxygen, using an appropriate dose of vecuronium as a neuromuscular blocking agent. A 20-gauge catheter was inserted into the radial artery to measure arterial pressure and collect arterial blood. While the concentration of isoflurane was kept at 1% and a stable haemodynamic state was maintained, NTG solution (5 mg in 40 ml of saline) was administered i.v. using an infusion pump (Syringe pump, model STC-525, Terumo Co., Tokyo) through an extension tube coated with non-absorbable silicone to prevent loss

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Hiroshi Aoki, MD, Toshiki Mizobe, MD, PhD, Masato Harada, MD, PhD, Hiroto Imai, MD, Atsuko Kobayashi, MD, PhD, Department of Anaesthesiology, Kyoto Prefectural University of Medicine, Kawaramachi-Hirokoji, Kamigyo-ku, Kyoto, Japan, 602. Michiko Inoue, PhD, Department of Pharmacology, Tokyo University of Pharmacy and Life Science, 1432-1 Horinouchi, Hachiouji, Tokyo, Japan, 192-03. Accepted for publication: June 3, 1997.

of NTG. Infusion of NTG was started at a rate of 1 μg kg^{-1} min^{-1}, which was increased until mean arterial pressure decreased to 50–65 mm Hg. The maximal infusion rate was chosen individually for each patient. NTG infusion was continued for no less than 1 h.

Arterial blood was obtained just before the start of infusion of NTG and 10 min after the maximal infusion rate was achieved. Blood was obtained in plastic tubes containing a 1:4 volume of acid citrate glucose solution (ACD) for measurement of platelet aggregation, intracellular calcium concentration and intracellular cGMP concentration. For measurement of concentrations of NTG and nitrite ions in plasma, 10-ml samples were anticoagulated with heparin 50 μl (50 u.). In order to investigate the effect of NTG on haemostasis, template bleeding times were measured in six patients before and 30 min after the start of infusion of NTG using Simplate (Organon teknica Co., Durham, NC, USA).

The control group consisting of seven patients (four men and three women, mean age 53.8 yr) also undergoing surgery of the hip joint, were anaesthetized using the same method but without infusion of NTG. Platelet aggregation, intracellular calcium concentration and template bleeding times were measured every hour during anaesthesia.

MEASUREMENT OF AGGREGATION AND INTRACELLULAR CALCIUM CONCENTRATION

Platelet rich plasma (PRP) was obtained as a supernatant after centrifugation of ACD-treated blood for 15 min at 800 rpm at room temperature. PRP was incubated with Fura-2 acetoxymethyl ester 3 mmol for 15 min at 37 °C and then centrifuged in the presence of apyrase 0.3 iu ml^{-1} at 1200 rpm for 15 min. Fura-2 loaded platelets were separated by discarding the supernatant and resuspended in Tyrode– Hepes buffer, pH 7.4.[11] Platelets were counted with a Coulter counter (Model T-540, Coulter Electronics Inc., Hialeah, Fla.) at a concentration of approximately 10^5 cells μl^{-1}. Contamination of the samples by leucocytes was less than 5% in all experiments. Intracellular calcium concentration ($[Ca^{2+}]_i$) and platelet aggregation were measured simultaneously with a calcium analyser (CAF-110, Jasco, Tokyo, Japan) with repeated alternating excitation wavelengths of 340 and 380 nm and measuring emission of 505 nm.[12] The platelet solution (490 μl) was adjusted so that the extracellular Ca^{2+} concentration was 1 mmol litre^{-1} by addition of $CaCl_2$ solution, and stirred for 5 min at 37 °C. After recording basal fluorescence intensity, platelets were stimulated with thrombin 0.01 iu ml^{-1}, and the change in fluorescence intensity was monitored for 6 min. Change in $[Ca^{2+}]_i$ was calculated as the relative ratio of fluorescence intensity at 340 nm to that at 380 nm ($R_{340/380}$).[13 14] Stimulation of thrombin-induced biphasic Ca^{2+} mobilization and the relative rates at the peak and at 6 min were recorded. $[Ca^{2+}]_i$ at each point was calculated according to the equation of Tsien, Rink and Poenie,[15] using K_d values of Fura-2 and Ca^{2+} of 224 nmol litre^{-1}. Data are expressed as increase in $[Ca^{2+}]_i$ from basal concentrations.

Aggregation measurements were performed according to the turbidimetric method of Born and Cross.[16] Inhibition of aggregation was measured as inhibition of light transmission at 6 min after addition of thrombin. All experiments were completed within 2 h of blood collection.

MEASUREMENT OF PLATELET CGMP CONCENTRATION

Concentrations of cGMP in platelets were measured by radioimmunoassay[17] using an RIA kit (Amersham International, Amersham, England). The washed platelet solution was added to the same volume of 20% trichloroacetic acid solution, then frozen immediately with dry ice and stored at −80 °C until the cGMP assay was done. Before performing the assay, cyclic nucleotides were extracted from the samples with ether and evaporated. The residues were dissolved in sodium acetate buffer 50 mmol litre^{-1} (pH 6.2) and acetylated with acetic anhydride and triethylamine (1:2) reagent. Data are expressed as pmol/10^9 platelets.

CONCENTRATION OF NITRITE ION AND NTG IN PLASMA

For measurement of nitrite ion concentration, plasma was deproteinized with 10% zinc sulphate solution and the supernatant was added to the same volume of Greiss reagent,[18] which forms a deep purple azo compound in the presence of nitrite ions. Absorbance intensity of the azo compound was measured at 540 nm using a 96-well microplate reader (Multiskan Biochromatic, Labsystems, Helsinki, Finland) with sodium nitrite solution as standard.

Plasma concentrations of NTG were measured using gas chromatography–negative ion chemical ionization–selected ion monitoring (GC–NICI–SIM) according to Idzu and colleagues,[19] with some modifications. The $[^3H_5, {}^{15}N_8]$ variant was used as an internal standard and 20 ng was added for each 2 ml of plasma. After deproteinization with Extrelut (#1003, Merck Co., Darmstadt, West Germany), NTG was extracted with n-hexane and purified on a Sephadex LH-20 column (Pharmacia Fine Chemicals, Uppsala, Sweden). A gas chromatography–mass spectrometry system (Japan Electron Optics Laboratory Ltd, Tokyo, Japan) was used with chloroform as the reagent gas.

MATERIALS

Apyrase (from potato) was obtained from Sigma Chemical Company, St Louis, MO, USA; Fura-2 AM from Dojindo Laboratories, Kumamoto, Japan; and nitroglycerin from Nihon Kayaku Co. Ltd, Tokyo, Japan. Thrombin was donated by Mochida Pharmaceutical Co. Ltd, Tokyo, Japan. All other compounds were purchased from commercial sources.

STATISTICAL ANALYSIS

Results are expressed as mean (SEM), with numbers of observations in parentheses. Statistical analyses were carried out using paired *t* tests, the level of significance being $P<0.05$. For analysis of the results of template bleeding time, the Wilcoxon signed rank test was used.

Results

Eight patients were given NTG solution i.v. at rates of 4–8 (mean 5.13 (SEM 0.52)) μg kg^{-1} min^{-1}. During infusion of NTG, mean systolic arterial pressure decreased from 77.5 (3.7) to 61.1 (2.7) mm Hg. Heart rate did not change after infusion of NTG (control, 87.0 (5.3) beat min^{-1}; during NTG infusion, 87.3 (7.6) beat min^{-1}).

PLATELET AGGREGATION AND $[Ca^{2+}]_i$

Platelet aggregation induced by thrombin 0.01 iu ml^{-1} was observed in all eight patients before infusion of NTG, and was inhibited in seven patients after infusion of NTG (table 1). Representative patterns of aggregation and change in the $R_{340/380}$ value (indicating a change in $[Ca^{2+}]_i$) are demonstrated in figure 1. The mean value of the change in $[Ca^{2+}]_i$ at the first peak induced by thrombin was 439.9 (68.7) nmol litre^{-1} in controls and 210.6 (38.7) nmol litre^{-1} after infusion of NTG ($P<0.05$). The mean value of the change in $[Ca^{2+}]_i$ at the second phase was 154.4 (19.8) nmol litre^{-1} in controls and 106.7 (18.0) nmol litre^{-1} after infusion of NTG ($P<0.05$). In contrast, seven patients who received nitrous oxide–isoflurane anaesthesia without infusion of NTG demonstrated no inhibition of platelet aggregation induced by the same dose of thrombin. The mean value of the change in $[Ca^{2+}]_i$ at the first peak was 491.9 (36.4) nmol litre^{-1} in controls and 460.3 (45.4) nmol litre^{-1} 1 h later. The mean value of the change in $[Ca^{2+}]_i$ at the second phase was 179.9 (22.8) nmol litre^{-1} in controls and 209.7 (44.6) nmol litre^{-1} 1 h after. These values were not significantly different.

Table 1 Platelet aggregation, changes in intraplatelet calcium concentrations and plasma concentrations of nitroglycerin. No=Platelets demonstrated no aggregation; Inhibited=platelets, although aggregated, were inhibited compared with control aggregation; Yes=platelets aggregated fully; NTG=Nitroglycerin, NTG concn=plasma concentration of nitroglycerin. Statistical comparisons by paired *t* test: $^{*}P<0.05$

		Ca-first phase (nmol litre^{-1})		Ca-second phase (nmol litre^{-1})			
Patient No.	Platelet aggregation	Control	NTG	Control	NTG	NTG concn (ng ml^{-1})	NTG dose (μg kg^{-1} min^{-1})
1	No	466.5	235.6	130.9	62.9	67	6
2	No	730.2	90.2	122.7	67. 5	15	4
3	No	449.2	213.1	171.9	109.4	27	4
4	No	681.2	120.3	78.3	50.7	No data	5
5	Inhibited	190.6	162.5	121.1	105.8	No data	4
6	Inhibited	223.2	259.1	218.6	136.4	32	6
7	Inhibited	332.5	291.5	240.0	210.0	41	8
8	Yes	445.6	396.1	68.5	110.5	51	4
Mean (SEM)		439.9 (68.7)	210.6 (38.7)*	154.4 (19.8)	106.7 (18.0)*	38.8 (7 5)	5.13 (0.52)

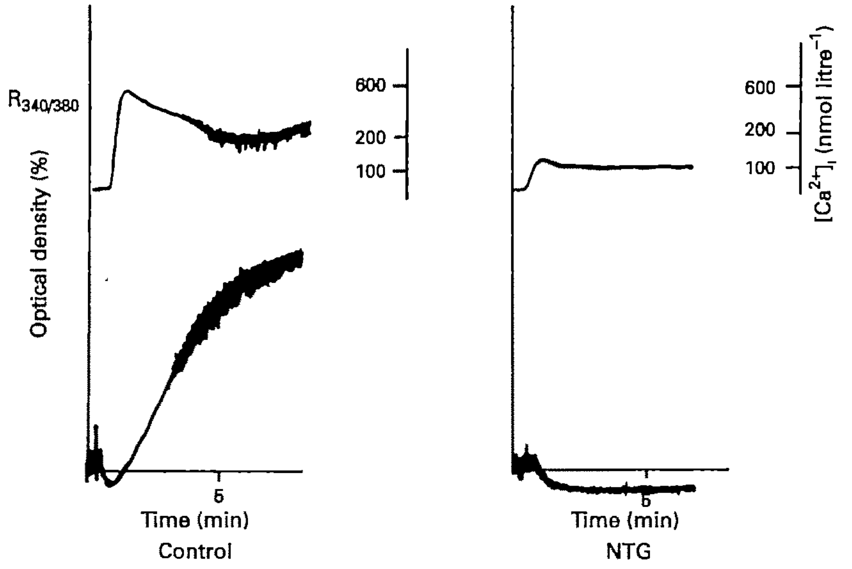

Figure 1 Platelet aggregation (lower panel) and changes in $R_{340/380}$ (upper panel) in controls (left) and during infusion of nitroglycerin (NTG, right). A representative profile (patient No. 4 in table 1) of the eight patients is shown. The ordinate at the right side represents the corresponding intraplatelet calcium concentration.

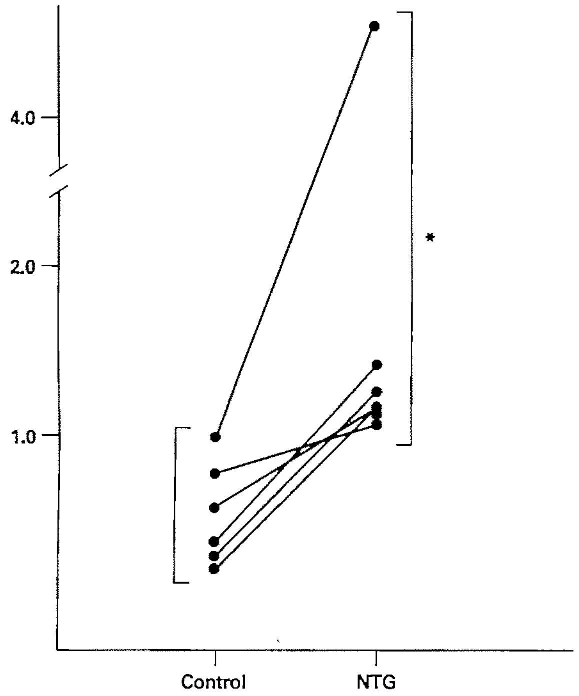

Figure 2 Changes in intraplatelet cGMP concentrations in controls and during nitroglycerin infusion (NTG) ($n=6$). Statistical comparisons by paired *t* test: $*P<0.05$.

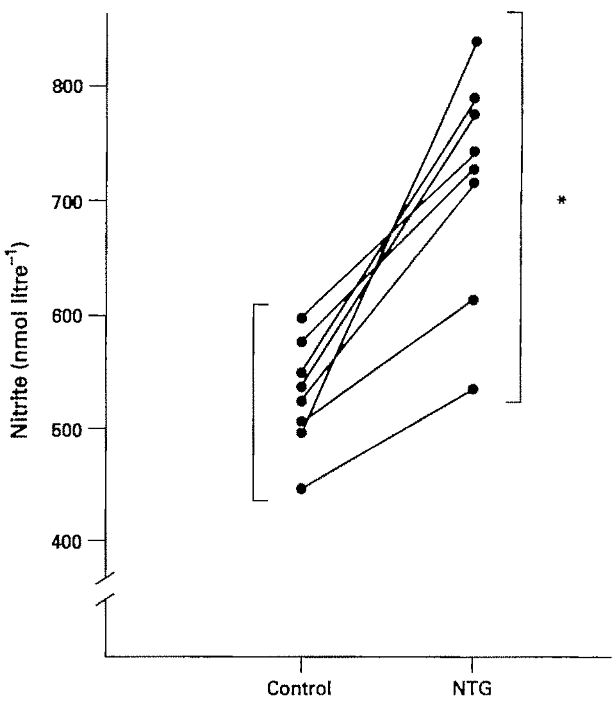

Figure 3 Changes in plasma nitrite ion in controls and during infusion of nitroglycerin (NTG) ($n=8$). Statistical comparisons by paired *t* test: $*P<0.05$.

CYCLIC GMP CONCENTRATION IN PLATELETS

The mean value of intracellular cGMP concentrations in platelets was 0.633 (0.098) pmol/10^9 platelets in the resting state, which increased significantly after infusion of NTG to 1.764 (0.578) pmol/10^9 platelets ($n=6$) (fig. 2). The increase in ratio ranged from 1.3- to 4.8-fold. Data were not obtained from two of eight patients.

PLASMA CONCENTRATIONS OF NTG AND NITRITE ION

During infusion, NTG concentrations in plasma ranged from 15 to 67 ng ml^{-1} (mean 38.3 (7.5) ng ml^{-1}) ($n=6$) corresponding to a concentration of the order of 10^{-8} mol litre^{-1}. Data were not obtained from two of eight patients.

Nitrite ion concentrations in plasma were measured before and during infusion of NTG. The mean concentration of nitrite ion before infusion was 532.6 (17.6) nmol litre^{-1} ($n=8$); after infusion, the mean value increased significantly to 724.4 (34.8) nmol litre^{-1} ($n=8$) (fig. 3). There was a correlation ($r^2=0.77$) between the increase in intraplatelet cGMP concentration and the increase in the concentration of nitrite ion.

TEMPLATE BLEEDING TIME

In six patients given NTG, template bleeding time was 8.38 (0.72) min before infusion of NTG and 8.25 (0.48) min during infusion (ns). In seven patients who received nitrous oxide–isoflurane anaesthesia, template bleeding time was 8.38 (0.72) min initially and 8.25 (0.48) min 30 min later (ns).

Discussion

In this study, we infused a large dose of NTG to induce hypotension, which resulted in increased intraplatelet cGMP concentrations and inhibition of increases in $[Ca^{2+}]_i$ and platelet aggregation. These changes may have been induced by increased concentrations of nitrite ion.

During activation, platelets show an increase in $[Ca^{2+}]_i$ and aggregation,[20] a process which may be modulated by intracellular cyclic 3', 5'-adenine monophosphate (cAMP) and cGMP.[21]

The inhibitory effect of NTG on the increase in $[Ca^{2+}]_i$ and platelet aggregation had been demonstrated in an earlier *in vitro* study.[22] Cyclic GMP was regarded as a mediator of the action: the increase in its intracellular concentration initiated the inhibitory process in platelets.[7] In contrast, in *in vivo* studies, infusion of NTG was reported to inhibit platelet aggregation,[23 24] although the precise mechanism by which platelet inhibition occurred was not investigated.

The effects of NTG on intraplatelet cGMP concentration, intracellular Ca^{2+} mobilization and aggregation were reported at NTG concentrations of approximately 10^{-4} mol litre^{-1} in *in vitro* studies.[6 22 25] Although we infused NTG at doses large enough to demonstrate clear decreases in arterial pressure, plasma concentrations of NTG only reached approximately 10^{-8} mol litre^{-1}. Kahlberg and colleagues' *in vivo* study[24] also showed that plasma concentrations of NTG were less than 10^{-8} mol litre^{-1}. Concentrations of NTG of the order of 10^{-8} mol litre^{-1} do not inhibit platelet function, according to the literature[7 10 22] and our previous *in vitro* pilot study (data not shown). The intracellular cGMP concentration and the increase in $[Ca^{2+}]_i$ were also reported not to be affected by the plasma concentration of NTG.[26] However, when platelets are incubated with reducible thiols, such as N-acetylcysteine, NTG-induced inhibition of platelet aggregation occurs at plasma NTG concentrations of the order of 10^{-8} mol litre^{-1}.[7] One *in vitro* study revealed that nitroso compounds reacted with thiols and formed S-nitrosothiols, which inhibited platelet aggregation.[27] Thereafter, liberation of nitric oxide from NTG was detected and this liberation was potentiated by added thiol.[28] S-nitrosothiols are regarded as active intermediates or carriers of nitric oxide.[29–31] Nitric oxide was also detected when NTG was incubated with vascular tissue[32,33] and it potentiated the increase in intraplatelet cGMP concentrations and inhibition of platelet aggregation.[34,35] The increase in the concentration of nitrite ion, the breakdown product of nitric oxide,[35] was also confirmed in our study. Accordingly, we proposed that nitric oxide was liberated as a consequence of bioconversion of NTG. This results in an increase in intraplatelet cGMP concentration and, simultaneously, inhibition of intracellular Ca^{2+} mobilization and platelet aggregation *in vivo*.

All data in this study were acquired during general anaesthesia with inhaled isoflurane in nitrous oxide. Therefore, we investigated the effects of these anaesthetics in seven patients and revealed that these anaesthetic procedures did not influence platelet function. Accordingly, inhibition of platelet aggregation and changes in intracellular calcium concentration which we demonstrated in this study were caused by NTG, although template bleeding time was not changed.

In summary, we have demonstrated *in vivo* that infusion of NTG increased cGMP concentrations in platelets and inhibited Ca^{2+} mobilization and platelet aggregation. Bioconversion of NTG was confirmed by the detection of a significant increase in nitrite ion in plasma. Therefore, nitric oxide could participate in the mechanism of these inhibitory effects. As the half-life of nitric oxide is reported to be very short, of the order of seconds,[36] these inhibitory effects should resolve promptly after cessation of infusion of NTG.

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Validity of acoustic quantification colour kinesis for detection of left ventricular regional wall motion abnormalities: a transoesophageal echocardiographic study†

T. HARTMANN, N. KOLEV, A. BLAICHER, C. SPISS AND M. ZIMPFER

Summary

Transoesophageal echocardiography is a sensitive monitor for intraoperative myocardial ischaemia. Colour kinesis is a new technology for echocardiographic assessment of regional wall motion based on acoustic quantification. We have examined the feasibility and accuracy of quantitative segmental analysis of colour kinesis images to provide objective evaluation of systolic regional wall motion during the perioperative period using transoesophageal echocardiography (TOE). Two-dimensional echocardiograms were obtained in the transgastric short-axis and long-axis views in 60 patients with coronary artery disease undergoing non-cardiac surgery. End-systolic colour overlays superimposed on the grey scale images were obtained with colour kinesis to colour encode left ventricular endocardial motion throughout systole. These colour-encoded images were divided into segments and compared with corresponding conventional two-dimensional images. Six hundred of a potential 720 left ventricular wall segments were of sufficient resolution for grading by experts; they diagnosed wall motion abnormalities in 61 of these segments by a conventional method. In comparing the conventional TOE method with colour kinesis, there were 60 true positives, 482 true negatives, 57 false positives and 1 false negative result. This yielded a sensitivity of 98%, specificity of 89%, positive predictive value of 51% and negative predictive value of 100%. Translational and rotational movement of the heart and papillary muscle interference were common problems accounting for false positive diagnoses. We conclude that colour kinesis provides a basis for objective and on-line evaluation of left ventricular regional wall motion which is a sensitive but non-specific method. It may be a useful aid for the less experienced because it can potentially direct the anaesthetist's attention towards specific segments. (*Br. J. Anaesth.* 1997; **79**: 482–487).

Key words
Monitoring, echocardiography. Monitoring, colour kinesis. Heart, ischaemia. Heart, ventricles. Heart, myocardial function.

Transoesophageal echocardiography (TOE) is a sensitive and specific monitor for intraoperative myocardial ischaemia in patients with coronary artery disease.[1–3] However, conventional assessment of wall motion, based on visual interpretation of endocardial excursion, is experience-dependent and subjective.[1] To facilitate more objective evaluation of left ventricular endocardial motion, colour kinesis, a new technique based on acoustic quantification, has been developed and incorporated into a commercial ultrasound system (Hewlett-Packard Sonos 2500 and Vingmed CFM 800). Recently, Lang and colleagues[4] reported that colour kinesis images provided accurate and quantitative diagnosis of regional wall motion abnormalities using a transthoracic approach. Therefore, we compared prospectively left ventricular segmental wall motion patterns assessed by experts with those of colour kinesis in patients at risk of myocardial ischaemia undergoing TOE during non-cardiac surgery.

Patients and methods

The study was approved by our Institutional Review Board and written informed consent was obtained from each patient. We studied 60 patients (39 males) with coronary artery disease (CAD), at risk of CAD or hypertensive heart disease, aged 42–79 yr (mean 53 yr) who were in sinus rhythm with a heart rate of 45–101 beat min^{-1} (mean 65 (SD 14) beat min^{-1}). All patients were ASA class II of the multifactorial index of cardiac risk in non-cardiac surgery with total predictive points of 6–12. The majority was undergoing peripheral vascular surgery. Criteria for entry into the study included the presence of one of the following: (a) defined CAD, as indicated by previous myocardial infarction, typical angina or atypical angina with an ischaemic ECG response to exercise, or scintigraphic evidence of a myocardial perfusion defect; (b) high risk of CAD, suggested by previous or current vascular surgery or the presence

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T. HARTMANN, MD, N. KOLEV, MD, T. A. BLAICHER, MD, C. SPISS, MD, M. ZIMPFER, MD, Department of Anaesthesiology and General Intensive Care, University Hospital of Vienna, Wahringer Gurtel 18–20, 1090 Vienna, Austria. Accepted for publication: May 29, 1997.

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of at least two of the following cardiac risk factors: age >65 yr, hypertension, current smoker, serum cholesterol >6.2 mmol litre^{-1} or diabetes mellitus. We defined a previous myocardial infarction using ECG Minnesota Code criteria. Typical angina was defined as a history of chest pain with at least three of the following four characteristics: substernal location, precipitation by exercise or stress, duration <15 min and resolution after rest or nitroglycerin treatment. Atypical angina required two of the characteristics in addition to an ischaemic ECG response to exercise. Patients were excluded if they had abnormal myocardial repolarization (e.g. left bundle branch block, digitalis effect, left ventricular hypertrophy) or non-ischaemic causes of abnormal wall motion (e.g. bundle branch block, ventricular pacing, prosthetic valve, myocarditis or infiltrative disorder of the left ventricle).[5] Patients were studied at the University Hospital of Vienna between June 1994 and May 1996.

Patients were premedicated with diazepam 0.15 mg kg^{-1} i.v., 1 h before surgery. Anaesthesia was induced with fentanyl 3 μg kg^{-1} and thiopentone 4 mg kg^{-1}. After orotracheal intubation facilitated by vecuronium 100 μg kg^{-1}, the lungs were ventilated with 60% nitrous oxide in oxygen. Anaesthesia was maintained with increments of fentanyl and vecuronium with isoflurane up to 1%. A 7.5-fibreoptic thermodilution catheter (American Edwards) was inserted via the subclavian vein and advanced to the distal pulmonary artery. Correct positioning for recording PCWP was confirmed by observing a clear change in the pressure waveform when the balloon was inflated, and by measuring oxygen saturation of blood at the tip of the catheter. Before induction of anaesthesia, PCWP was measured during normal respiration, and after induction it was measured while the patient's lungs were disconnected temporarily from the ventilator.

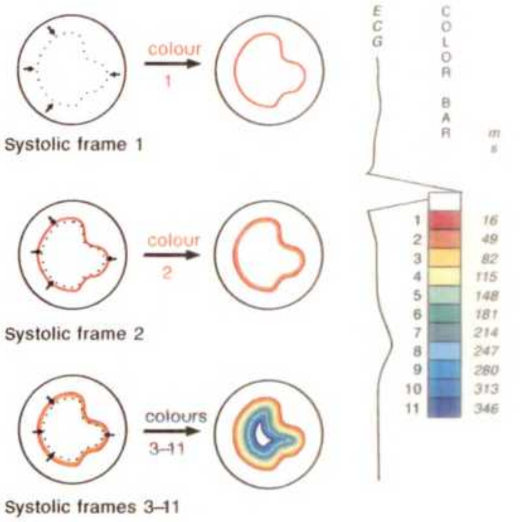

Figure 1 Principles of colour kinesis. The first frame is triggered with a delay from the R-wave to coincide with the start of left ventricular contraction and is assigned a colour which fills the space up to the border detected by the second frame. Successive frames are assigned different colours in sequence, as shown by the colour bar, and the spaces between successively detected borders are filled appropriately to give a composite multicolour rim that records the motion of different points on the circumference of the ventricular cavity during the time taken for the 11 frames.

COLOUR KINESIS: DESCRIPTION OF THE METHOD

Colour kinesis is an extension of the technology of acoustic quantification which uses changing values of tissue back-scatter between successive acoustic frames as a means of automatically tracing and displaying endocardial motion in real time. Acoustic quantification (Hewlett-Packard) has recently been validated against a variety of techniques by numerous investigators.[6 7] Colour kinesis processes the ultrasound back-scatter data and generates a binary mask image for each frame in which each pixel is classified as either blood or tissue. The pixel values at the transition from blood to tissue in this mask image are used to track systolic endocardial motion. The first frame in each cardiac cycle is triggered with a delay after the R-wave of the ECG so that it coincides with the start of inward movement of the left ventricular wall. The delay has a heart rate related default value but may need some visual–manual fine-tuning in some circumstances. Ten more frames follow the first successive intervals of 33 ms as the left ventricle contracts. The area between each new image of ventricular blood and the corresponding image in the preceding frame is filled with different shades of colour (fig. 1, left) superimposed on the grey scale image. A series of more or less concentric but irregular rims of colour accumulate from frame to frame in a way that reflects the time–motion history of endocardial excursion over the first 363 ms of the cardiac cycle (which usually covers most of the interval between isovolumic contraction and end-systole). The sequence of colours is indicated by the colour bar, with early systole being red–orange and late systole blue–purple (fig. 1, right): a default red in the image and in a signal box in the colour bar indicates outward segmental movement during systole (paradoxical motion). The width of any colour rim at any part of its circumference shows how much that portion of ventricular wall has moved inwards during the corresponding 33-ms inter-frame interval. The overlay of all 11 preceding colours on the last frame provides a multicoloured integrated display of the timing and magnitude of the inward motion of all endocardial segments during the 363 ms of the most recent systole. Thus the end-systolic width of the composite rim of colours represents the overall wall motion during most systoles. The display is updated beat by beat.

DATA ACQUISITION

Immediately after tracheal intubation, a multiplane probe with a 5-MHz phased-array transducer (Hewlett-Packard) was inserted into the oesophagus. The transducer was positioned and maintained at the level of the midpapillary muscles to obtain a short-axis view (T-scan) of the left ventricle and by steering the transducer to 90° to obtain a long-axis view (L-scan). The images were recorded on

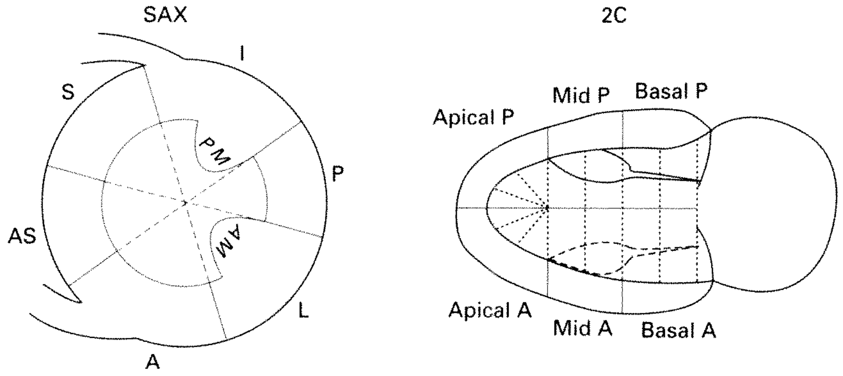

Figure 2 Segmentation schemes used for quantifying segmental analysis of endocardial wall motion according to the new recommendation of the American Society of Echocardiography. Short axis view (SAX) (transgastric): A=anterior; AS=anteroseptal; I=inferior; L=lateral; P=posterior; S=septal. (PM=posteromedial papillary muscle; AM=anterolateral papillary muscle). Longitudinal two-chamber view (2C) (transgastric): P=posterior; A=anterior.

videotape (Panasonic model AG-7350) for off-line analysis. After the image quality was optimized, the acoustic quantification system for endocardial border detection was activated. Gain controls (total and lateral gain, time-gain compensation) were adjusted to optimize tracing of the blood–endocardial interface within a preferred region of interest.[6] Colour kinesis was then activated for on-line encoding of endocardial excursion throughout systole. Image sequences containing colour kinesis data were obtained throughout the cardiac cycle and stored in a digital format for off-line analysis.

DATA ANALYSIS

Digital images were revived off-line using the continuous loop review mode of the echocardiographic system to ensure accurate tracking of the endocardial borers. In the transgastric short-axis view (T-scan), the segmentation originated from the left ventricular end-systolic cavity centroid. The zero degree line was defined by the centroid and a manually determined landmark represented by the junction between the right ventricular posterior wall endocardium and the interventricular septum.[9] The left ventricle was divided into six wedge-shaped sectors according to the new recommendations of the American Society of Echocardiography[10] (fig. 2, left). In the transgastric two-chamber views (L-scan), each image was divided initially into two sectors separated by a line (defined as the long-axis) connecting the distal apical endocardium with the end-systolic cavity centroid. Then, a series of perpendicular chords to the long axis of the ventricle, from the base to the midventricle, and a series of radii from the midpoint of the long axis of the ventricle to the apex, were constructed[8] (fig. 2, right). This scheme excluded mitral valve motion from the analysis.[9]

The type of colour kinesis throughout total ventricular systole was evaluated by reviewing the stored digital loops obtained in all patients. The fixed axis reference system was used for analysis.[8 11] The radial shortening of each segments as assessed by conventional two-dimensional images and colour overlay, was graded and scored (table 1).

All two-dimensional images were graded independently by two investigators using consensus, according to our laboratory published data[2]; these investigators were blinded to patient identity or colour kinesis. Colour kinesis detecting endocardial motion in each segment was measured off-line by a third blinded reader using callipers. To determine the effects of inter-examination variability, 200 scrambled samples from randomly chosen patients were re-read by the same observes, by consensus, approximately 2 months after the first reading.

STATISTICAL ANALYSIS

Data are given as mean (SD). Scores from colour-encoded acoustic quantification were compared with those derived by an experienced echocardiographer from two-dimensional images alone using correlation and simple regression analysis. Inter-observer

Table 1 Grading and scoring of the radial shortening of each segment, as assessed by conventional two-dimensional images and colour overlay

Class of motion	Conventional two-dimensional radial shortening	Colour kinesis		Scores
		No. of colours	Width of colour overlay	
Normal motion	>30%	11–9 colours	≥5 mm	1
Mild hypokinesis	10–30%	8–4 colours	<5 mm but >3 mm	2
Severe hypokinesis	>0 but <10%	3–1 colours	<3 mm	3
Akinesis	0	No colours		4
Dyskinesis	Systolic lengthening or bulging out	Red box on the colour bar		5

variability for each method was also evaluated. Difference were considered significant at $P<0.05$. The significance of differences in inter-observer interpretation of segmental systolic wall motion with two-dimensional echocardiography and the inter-technique (colour-encoded acoustic quantification) variability were compared for the proportions of pairs; 95% confidence intervals were estimated by $P \pm 1.96\, P\,(P-1)\, n$.

CALCULATIONS

Sensitivity=true positive/(true positive+false negative); specificity=true negative/(true negative+false positive); positive predictive value=true positive/all positives; and negative predictive value=true negative/all negatives.

Results

A total of 600 left ventricular wall segments were of sufficient resolution for grading by experts. Frame-by-frame analysis showed that the normal regional time of contraction ranged between 185 and 255 ms and was found to be consistent with inter-segment variations. Figure 3 gives an example of a normal contracting left ventricle from a transgastric short-axis view showing all 11 colours. In patients with hypokinesis there were reduced numbers of colours on the end-systolic overlay and thus reduced colour width/rim (fig. 4). In the majority of cases, endocardial shortening occurred early in systole. When no motion occurred, that is akinesis, the colour was absent. In figure 5, in the lateral segment of the left ventricular short-axis image, the colour rim shows outward systolic wall movement, for example paradoxical pixel transitions, and are all assigned the same red colour, regardless of the timing of transitions. It is evident that the colour bars are not quite the same in figures 3 and 4, compared with figure 5. In particular, in the lower part of the colour bar in figure 5 there is a red box which indicates that the "dyskinesis" feature is turned on, while in the images in figures 3 and 4 it is off. In fact, the statement that the colour bar reflects the timing of the endocardial motion is no longer the case for the paradoxical pixel transitions which are assigned

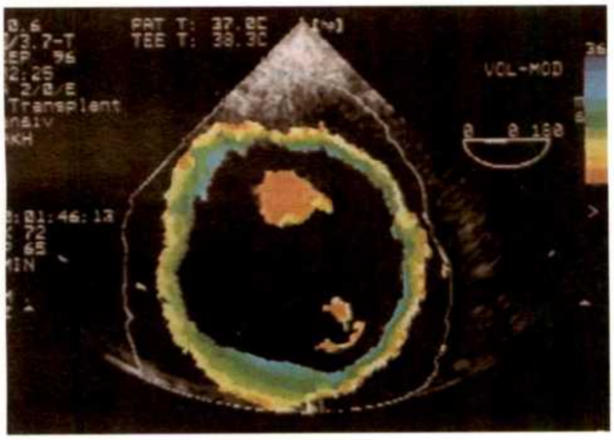

Figure 3 On-line assessment of regional wall motion using Hewlett-Packard colour kinesis technology. End-systolic colour-encoded image obtained in a normal subject in the transgastric short-axis view.

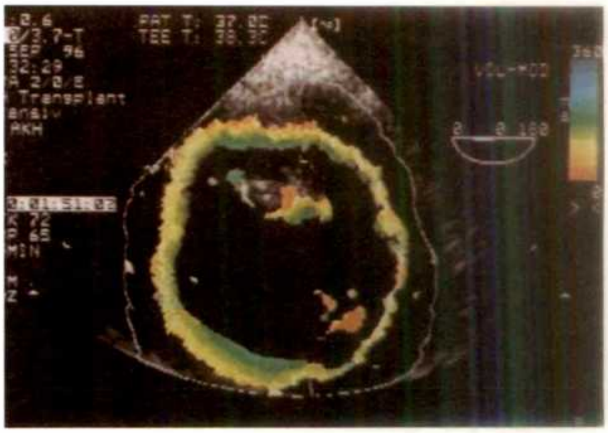

Figure 4 Example of colour kinesis data obtained from a patient with mild and severe hypokineis in the lateral and posterior segments of the left ventricular transgastric short-axis view.

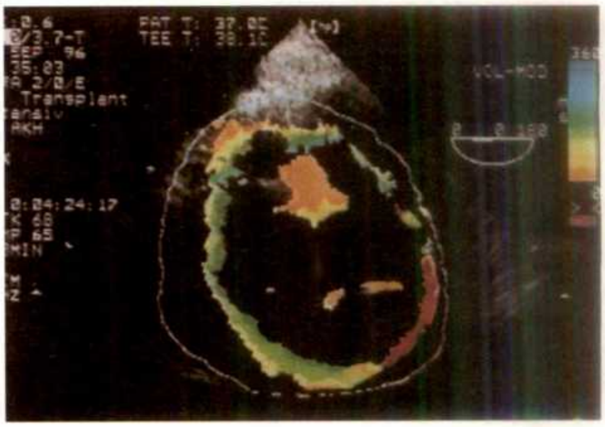

Figure 5 Example of colour kinesis data obtained from a patient with left ventricular dyskinesis showing outward systolic wall movement in the lateral segment (red) of the left ventricular transgastric short-axis scan. Note that there is a red box on the colour bar which indicates that the "dyskinesis" feature is turned on.

Table 2 Analysis of 600 left ventricular wall segments of which 61 showed conventional TOE-defined segmental wall motion abnormalities compared with whether the colour kinesis correctly diagnosed segmental wall motion abnormalities

	Conventional TOE		True positive	True negative	False positive	False negative	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative predictive value (%)
	Ischaemia	No ischaemia								
Colour kinesis			60	482	57	1	98	89	51	100
Ischaemia	60	57								
No ischaemia	1	482								

the same red colour, regardless of the timing of transition.

Wall motion abnormalities were found in 61 of 600 segments by a conventional method. Comparing the conventional TOE method and colour kinesis, there were 60 true positives, 482 true negatives, 57 false positives and 1 false negative. This yielded a sensitivity of 98%, specificity of 89%, positive predictive value of 51% and negative predictive value of 100% (table 2). Inter-observer variability in the interpretation of regional systolic wall motion based on two-dimensional echocardiograms was 13.5%. The inter-technique variability between the conventional interpretation of two-dimensional echocardiograms and the above-described automated detection was found to be 26.2% ($P<0.05$).

Discussion

We have described our initial experience with a new technique, colour kinesis, designed to evaluate online ventricular regional wall motion patterns using TOE during operation. We chose to use a fixed reference system to analyse end-systolic conventional two-dimensional and colour kinesis images. This choice was made because colour kinesis adopts a fixed reference system for tracking endocardial motion by identical pixels in successive acoustic frames; in other words, a fixed frame of reference is used when colour kinesis images are created. Moreover, as each pixel in the colour overlay cannot be assigned more than one value, information regarding multiple pixel transition resulting from translation and rotation is not reflected in the end-systolic colour overlay. Although no consensus exists, floating reference systems have been recommended when attempting to quantify regional wall motion in the presence of translation.[11 12] These systems use superimposition of a systolic and diastolic centroid. When regional wall motion abnormalities are present, however, the systolic centroid is displaced towards the abnormality, thereby exaggerating the apparent wall motion in affected regions and diminishing the apparent wall motion in adjacent regions.[13 14] Because of this phenomenon, floating reference systems do not localize regional wall motion abnormalities as well as fixed reference systems in the absence of translation.[9]

This study demonstrated that colour kinesis correctly diagnosed 60 of 61 segmental wall motion abnormalities. Tracking of papillary muscles, instead of endocardium, accounted for one failure. However, colour kinesis falsely diagnosed 57 other segmental wall motion abnormalities. Translation and rotational movement of the heart, and prolongation of the pre-ejection period (in cases of ischaemia[8]) were common problems causing false positive diagnoses.

Recently, Lang and colleagues[4] used a transthoracic approach and colour kinesis (Hewlett-Packard), dividing colour-encoded images into segments using custom software. In each segment, pixels of different colours were counted and displayed as stacked histograms reflecting the magnitude and timing of regional endocardial excursion. The same authors found that histograms were highly consistent and reproducible in normal subjects. The patterns of contraction obtained in normal subjects were used as a reference for the objective automated interpretation of regional wall motion abnormalities, defined as deviations from this pattern. The inter-technique variability between the conventional interpretation of two-dimensional echocardiograms and the above-mentioned automated detection was found to be 17.0%. This inter-technique variability was not significantly different from the inter-observer variability of the conventional interpretation. They concluded that segmental analysis of colour kinesis images provided accurate quantitative diagnosis of regional wall motion abnormalities.

The time resolution of colour kinesis is limited to 33 ms by the present frame rate of 30 frames per second. This restricts the definition of endocardial motion at increased heart rates so that it is not accurate enough to provide sufficiently exact indices of regional motion of the left ventricular endocardium. On the other hand, the limited number of colours currently available for encoding may confound accurate acquisition in patients with heart rates less than 45 beat min^{-1} because the 363 ms duration of colour encoding may not be sufficient to cover enough of the systolic period. These limitations could be overcome by using faster frame rate imaging, together with an extended colour scale.

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LABORATORY INVESTIGATIONS

Repeated enflurane anaesthetics and model predictions: a study of the variability in the predictive performance measures

P. M. VERMEULEN, J. G. C. LEROU, R. DIRKSEN, L. H. D. J. BOOIJ AND G. F. BORM

Summary

We quantified the total variability (reproducibility) and the within-patient but between repeat anaesthetics variability (repeatability) in measures which are used to judge the predictive performance of our physiological model. We studied 14 patients who received enflurane closed-circuit anaesthesia on two occasions. The end-tidal concentrations measured and those predicted served to calculate the predictive performance measures of the model: root mean squared error (rmse=total error), bias (systematic error) and scatter (error around the bias). The overall results were: rmse 15 (7) %, bias 0 (14) % and scatter 9 (3) % (grand mean (total SD)). The within-patient SD values were smaller for the rmse (4%) and bias (10%), but not for scatter (3%). The repeat rmse values and biases were linked to the first results. This implies that these performance measures depended partly on the patient. As there was no association between the personal performance measures and age, sex, body weight, body surface area or body mass index, these characteristics cannot be used to further tune the model. (*Br. J. Anaesth.* 1997; **79**: 488–496).

Key words
Anaesthetics volatile, enflurane. Equipment, breathing systems. Pharmacokinetics, models. Model, physiological.

Using average values of physiological variables and physicochemical data, we have defined a physiological model for closed-circuit inhalation anaesthesia.[1] It is capable of predicting end-expired concentrations after injection of a liquid anaesthetic into a closed-circuit breathing system. Previously we have evaluated the predictive performance of the model by examining the differences between the concentrations predicted and those measured in surgical patients. The observed prediction errors were condensed, per patient, into three single performance measures. These identify the total error size (rmse), systematic error (bias) and error around the bias (scatter). Close agreement between predictions and measurements was found in groups of patients anaesthetized with different volatile anaesthetics.[2–4]

Yet, if we wish to apply a model in a particular patient to predict the concentrations of a drug, variability in pharmacokinetic responses must be taken into account. Until now our clinical studies have provided information only on the between-patient variability, expressed in terms of variability in the predictive performance measures of the model, because different patients were studied only once. A major unresolved issue was the repeatability of the performance measures of the model in a patient presenting for repeated anaesthetic procedures.

Therefore, we studied patients who underwent enflurane closed-circuit anaesthesia twice. The objectives were: to evaluate the extent of correspondence between the predictive performance measures of the model obtained in the same patient on two occasions under similar clinical conditions; to determine if these measures varied more among than within patients; and to assess the association of the performance measures of the model with patient characteristics.

Patients and methods

Part of the methods has been described in detail previously and is summarized here together with the details necessary for this specific study.[1–4]

PATIENTS AND ANAESTHETIC MANAGEMENT

Earlier we completed a validation study of our system model for enflurane closed-circuit anaesthesia in 50 patients. They underwent elective eye surgical procedures, and 15 needed a second surgical intervention of the same type. After approval of the Institutional Ethics and Research Committee, these 15 consenting, Caucasian patients (ASA I or II) were enrolled in the study.

First anaesthetic procedure

Diazepam 5–10 mg and droperidol 2.5–5 mg were given orally 1 h before surgery. Anaesthesia was

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P. M. VERMEULEN*, MD, J. G. C. LEROU, MD, PHD, R. DIRKSEN, MD, PHD, L. H. D. J. BOOIJ, MD, PHD, FRCA (Institute for Anaesthesiology); G. F. BORM, PHD (Department of Medical Statistics); University of Nijmegen, The Netherlands. Accepted for publication: May 28, 1997.

*Address for correspondence: Institute for Anaesthesiology, University of Nijmegen, Geert Grooteplein 10, 6500 HB Nijmegen, The Netherlands.

induced with fentanyl 0.1–0.2 mg i.v. and a dose of thiopentone sufficient to abolish the eyelash reflex. Thereafter, vecuronium 0.1 mg kg^{-1} i.v. was administered. After placement of a cuffed tracheal tube, the lungs of the patients were ventilated artificially with a high fresh gas flow of oxygen and nitrous oxide in a 1:2 ratio until the end-tidal nitrogen concentration was less than 1 vol% or for a maximum of 5 min. Subsequently, the anaesthetic system was closed and closed-circuit anaesthesia commenced. The fresh gas flow of oxygen and nitrous oxide was adjusted manually to maintain the inspired oxygen concentration at 30–40 vol%. The end-tidal carbon dioxide concentration was 4.0–5.0 vol%.

Enflurane anaesthesia was administered using the liquid injection method by the same anaesthetist (P. M. V.). Boluses of liquid enflurane were injected into the expiratory limb of the system: one of 0.02 ml kg^{-1} (±0.1 ml) after the start of closed-circuit conditions and repeated increments of 0.01 ml kg^{-1} during maintenance. We did not use a rigid drug regimen, but modified enflurane administration to provide adequate anaesthesia as in good clinical practice. Therefore, we monitored carefully the patient's response to surgery by assessment of non-invasive arterial pressure measurement, heart rate and heart rate variability judged by ear with the aid of pulse oximetry, and also end-tidal enflurane concentration. Additional i.v. fentanyl 0.05–0.1 mg was given according to clinical needs.

Second anaesthetic procedure

This was separated from the first by at least 2 weeks. Patients received the same premedication. Anaesthesia was induced and maintained as described above. The same parameters for mechanical ventilation (frequency, tidal volume) were used. By design we did not aim to replicate the timetable of enflurane injections from the first anaesthetic. As in the first anaesthetic procedure, individual's anaesthetic needs under given surgical conditions prevailed as necessary.

For both procedures, we noted the times and volumes of liquid enflurane, and total volume administered (ml), and computed the average measured end-tidal enflurane concentration (vol%). To evaluate our anaesthetic management, we also expressed the average measured end-tidal enflurane and nitrous oxide concentrations as multiples of MAC corrected for age (mMAC) and calculated their sum (i.e. total mMAC).[5] Before evaluating the anaesthetic requirements and calculating the errors of prediction, we curtailed one of the two data files per patient, that is the one with the longest duration. Thus we considered only repeated observations for exactly the same duration.

INSTRUMENTATION

The anaesthetic equipment consisted of an Ohmeda Modulus CD anaesthesia system (Madison, WI, USA) with a standing bellows ventilator (Ohmeda 7850). The delivered tidal volume depends on the rate of fresh gas flow into the standing bellows ventilator.[6] Consequently, reducing and adjusting the fresh gas flow in order to provide closed-circuit conditions mostly necessitated frequent adjustments of tidal volume and the flowmeters at the beginning of closed-circuit anaesthesia. Five minutes were required until we were confident that tidal volume was equal during repeated measurements. Therefore, we only analysed data acquired after this initial non-steady state period.

A respiratory mass spectrometer (Centronic 200 MGA or QP9000; CaSE, Gillingham, England) continuously sampled gas at the Y-piece of the anaesthetic circuit via a side-stream sampling port (the sample flow is part of the model). The coefficient of variation of the mass spectrometer readings was 2%. Before starting each measurement we verified calibration of the mass spectrometer for enflurane with a calibration gas mixture containing 1% enflurane in 30% oxygen, 30% nitrous oxide and balance gas nitrogen (AGA Gas, Amsterdam, The Netherlands).

A personal computer system with a 12-bit analogue-to-digital board (Keithley Metrabyte, Taunton, MA, USA) processed the signals from the mass spectrometer. The data acquisition software was developed with the aid of ASYST (Keithley Metrabyte). On-line analysis of the respiratory waveforms allowed continuous monitoring in the operating room of the actual inspired and end-expired concentrations of nitrogen, oxygen, carbon dioxide, nitrous oxide, argon and enflurane. The trends of the inspired and end-expired concentrations of enflurane and oxygen of the last 20 min were also displayed continuously. The last end-expired enflurane concentration was saved for each 10-s period for further data processing.

THE MODEL AND ITS INPUT

The end-expired concentrations measured were compared with those predicted by our system model, version C, which does not assume a zero circulation time and accounts for non-pulmonary elimination of the anaesthetic agent.[3] Details of the model and its components are given in appendix 1. Data processing was a three-step process. During step one, the model input was generated by means of an ASYST application program. The model input consisted of

Table 1 Predictive performance measures: pe=prediction error (%), *n*=number of measurements per patient, pe_i is the *i*-th prediction error and me=mean prediction error. C_p and C_m=*p*redicted and *m*easured end-tidal concentrations of enflurane

$\text{pe}=\frac{C_p-C_m}{C_m}\times 100$	=Prediction error per pair of predicted and measured values
$\sqrt{\frac{1}{n}\sum_{i=1}^{n}\text{pe}_i^2}$	=Rmse $=\sqrt{(\text{Bias}^2+\text{scatter}^2)}$ total error budget
$\text{me}=\frac{1}{n}\sum_{i=1}^{n}\text{pe}_i$	=Bias systematic component of the error
$\sqrt{\frac{1}{n}\sum_{i=1}^{n}(\text{pe}_i-\text{me})^2}$	=Scatter dispersion of the errors (pe) around their mean (me)

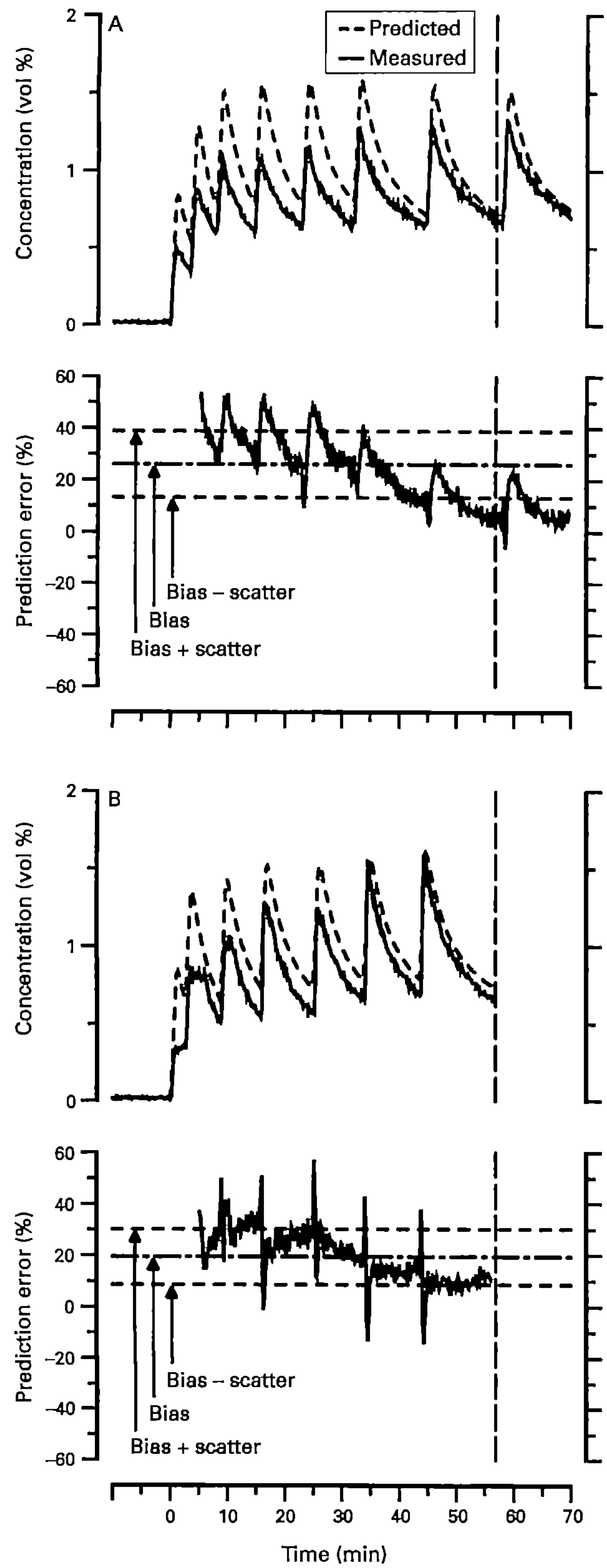

Figure 1 Repeated observations from a 22-yr-old female patient (weight 67 kg, height 1.75 m). A: Predicted and measured end-tidal enflurane concentrations, and prediction errors obtained during the first anaesthetic: one per 10-s period. The observed prediction errors were condensed into three predictive performance measures: total error size (rmse), systematic error (bias) and error around the bias (scatter). These were 29.0%, 26.1%, and 12.8%, respectively. B: The same variables as in (A) obtained during the repeated procedure. Rmse, bias and scatter were 22.2 %, 19.4 % and 10.8 %, respectively. The patient was anaesthetized with 7.0 ml of liquid enflurane administered in seven injections on both occasions. The vertical broken line shows how the data file with the longest duration was curtailed to match the durations of both anaesthetics.

patient data (age, sex, body weight and height) and the enflurane dosing schedule (timetable of injections with the amount of each enflurane increment). The amount of liquid enflurane per injection was converted into millilitres of vapour and supplied to the model as if the vapour were added to the anaesthetic system over a 60-s interval (i.e. the average time period necessary for the enflurane liquid to evaporate).

Throughout step two, our model generated the predicted time courses of the end-expired enflurane concentrations by running a TUTSIM simulation program (Meerman Automation, Neede, The Netherlands). In the final step three, by importing the predicted and measured data into another ASYST application program, the predictive performance measures of the model (see below) were calculated. For each patient and each anaesthetic procedure we predicted the end-expired concentrations by applying our system model.

PREDICTIVE PERFORMANCE MEASURES

Table 1 summarizes the measures which serve to determine the predictive performance of our model. The prediction error (pe) is the difference between a predicted and measured value of enflurane concentration, expressed as a percentage of the measured value: pe and squared prediction error (pe^2) are calculated for each time period of 10 s. These two quantities are used to provide the following three predictive performance measures.

(1) Root mean squared error (rmse). The mean squared error (mse) is the average of the squared prediction errors. Rmse is defined as $\sqrt{mse}$ and is a measure of the total error budget for an individual patient during one anaesthetic procedure. It is not influenced by the sign of the prediction errors and can be formulated as being composed of bias and scatter (table 1).

(2) Bias, that is the average of the prediction errors for an individual patient, is a measure of the systematic component of error. It can be either positive or negative, thus indicating over prediction or under prediction, respectively.

(3) Scatter is a measure of the variation of the prediction errors around their mean (bias) during one procedure.

These three measures were calculated for the first and the repeat anaesthetic procedure. Thus per patient we had a first and repeat rmse, bias and scatter, as illustrated in figure 1.

VARIABILITY MEASURES

The measures we used to describe the variability in the predictive performance measures were in accordance with the recently updated reports of the International Organization for Standardization ISO-5725, part 1 and 2, for repeated measurements.[7 8] Detailed information is given in appendix 2 and a summary follows. Three variances are calculated for each of the three performance measures (fig. 2).

(1) Within-patient (or repeatability) variance

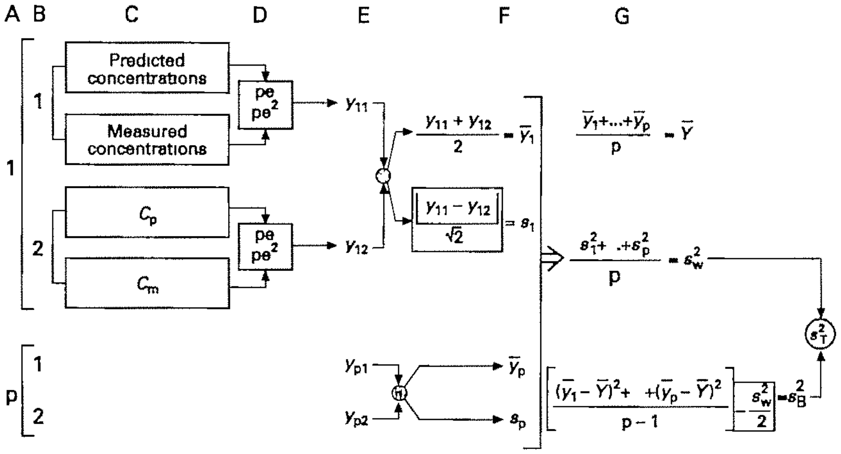
A
B
C
D
E
F
G
1
1
2
p
1
2
Predicted concentrations
Measured concentrations
C_p
C_m
pe
pe^2
y_{11}
y_{12}
y_{p1}
y_{p2}
$\frac{y_{11}+y_{12}}{2} = \bar{y}_1$
$\frac{|y_{11}-y_{12}|}{\sqrt{2}} = s_1$
$\bar{y}_p$
s_p
$\frac{\bar{y}_1+...+\bar{y}_p}{p} = \bar{Y}$
$\frac{s_1^2+...+s_p^2}{p} = s_W^2$
s_T^2
$\left[\frac{(\bar{y}_1-\bar{Y})^2+...+(\bar{y}_p-\bar{Y})^2}{p-1} - \frac{s_W^2}{2}\right] = s_B^2$

Figure 2 Flow diagram for calculating the predictive performance measures of the model (columns A–E) and their variability measures (columns F–G) from p patients: A. patient number, B: number of anaesthetics; C: predicted (C_p) and measured (C_m) end-tidal enflurane concentrations. one per 10-s period; D: prediction error (pe) (%) and squared prediction error (pe^2): one per 10-s period; E: three predictive performance measures: rmse, bias and scatter, any one of these results given by y with the appropriate subscripts for patient and anaesthetic; F: mean ($\bar{y}$) and standard deviation (s) of each performance measure in a patient (mathematical expressions simplified for the particular case of two observations); G: grand mean of each of the predictive performance measures ($\bar{Y}$), with the within-patient (s^2_W), between-patient (s^2_B) and total (s^2_T) variance.

(s^2_W) is the average of individual variances. It is an indicator of the variation in a predictive performance measure within a patient (between repeat anaesthetics). The within-patient variability can yield an estimate of an expected performance measure for an individual from other values obtained in the same patient during former anaesthetics (=repeatability).

(2) Between-patient variance (s^2_B) is an indicator of the variation in the patient means around the grand mean.

(3) Total (or reproducibility) variance (s^2_T) combines the within- and between-patient variances: it reflects the overall variation in a predictive performance measure in the sample population. The total variability observed in all patients is the variability associated with estimating one of the performance measures for a random "unexplored" patient from the grand mean (=reproducibility). In the clinical environment this is the variability encountered most frequently.

Repeatability, between-patient and reproducibility SD (SD_W, SD_B, SD_T) were also calculated for each of the performance measures.

STATISTICAL METHODOLOGY

Graphical analysis of the data preceded formal statistical analysis. An analysis of variance was used for the predictive performance measures to calculate the components of variance according to Armitage and Berry.[9] Multiple regression analysis was used to study the association of age, sex, body weight, body mass index (BMI=weight height^{-2}) and body surface area (BSA, formula of DuBois and DuBois) with the average of the two repeated performance measures obtained per patient. The criterion for rejection of the null hypothesis was $P<0.05$ (two-sided).

Results

Initially, we studied 15 patients but data from one patient (original subject No. 10) were excluded from analysis. This patient had an extreme oculocardiac reflex during the second ophthalmic procedure requiring intervention. The clearly dissimilar clinical conditions (first *vs* repeat anaesthetic) yielded deviating results for rmse (8.44 *vs* 38.29%) and bias (3.14 *vs* 36.03%) although less for scatter (7.83 *vs* 12.95%), and precluded a meaningful analysis. Thus results of nine males and five females were analysed: mean age, body weight, BMI and BSA were 37.9 (range 14–66) yr, 71.8 (SD 10.4) kg, 22.6 (2.7) kg m^{-2} and 1.89 (0.15) m^2, respectively. Mean

Table 2 Details of the closed-circuit conditions and predictive performance measures (mean (SD)). n=14 for the first and repeat anaesthetic; n=28 for the grand mean results (third column). Total mMAC=sum of the average measured end-tidal enflurane and nitrous oxide concentrations, expressed as multiples of MAC corrected for age[5]

	First anaesthetic	Repeat anaesthetic	First and repeat anaesthetic
No. of injections	8.1 (2.1)	7.6 (1.4)	7.9 (1.8)
Injections per hour	8.7 (2.3)	8.1 (1.0)	8.4 (1.8)
Volume of liquid enflurane (ml)	7.2 (1.0)	7.0 (1.2)	7.1 (1.1)
Volume of liquid enflurane per hour (ml)	7.7 (0.9)	7.4 (1.0)	7.5 (1.0)
Average measured end-tidal enflurane (vol%)	0.98 (0.10)	0.93 (0.14)	0.95 (0.12)
Total mMAC	1.09 (0.13)	1.06 (0.12)	1.07 (0.12)
Rmse (%)	14.63 (7.43)	15.75 (6.76)	15.19 (7.09)
Bias (%)	−1.77 (13.23)	1.65 (15.08)	−0.06 (14.10)
Scatter (%)	9.47 (3.29)	8.53 (2.09)	9.00 (2.75)

duration of closed-circuit anaesthesia was 57.5 (12.9) min. Altogether these patients provided 9654 samples of intraoperative data and they were anaesthetized with a total of 198 ml of liquid enflurane for more than 27 h. Details on the repetitive closed-circuit conditions, recorded in table 2, corroborate that the closed-circuit conditions during both anaesthetics matched well. Only minor differences in the time schedules of the enflurane bolus injections were found. Table 2 also lists the predictive performance measures obtained from the first and repeat anaesthetic, and from the pooled data. The results from the latter data were: rmse 15 (7) %, bias 0 (14) % and scatter 9 (3) % (grand mean (SD$_T$)).

GRAPHICAL ANALYSIS

Simple scattergrams can be used to illustrate the association between the first and repeated observation on each of the performance measures.

(1) Figure 3A (left) demonstrates good agreement between repeated observations for total error size. Visual assessment of the extent of agreement between the two results is aided by the line of identity and a zone where the repeated observations differ by no more than ±5%. The maximum difference is approximately 11% (patient No. 12). Figure 3A (right) illustrates that the within-patient repeatability is not associated with the size of the

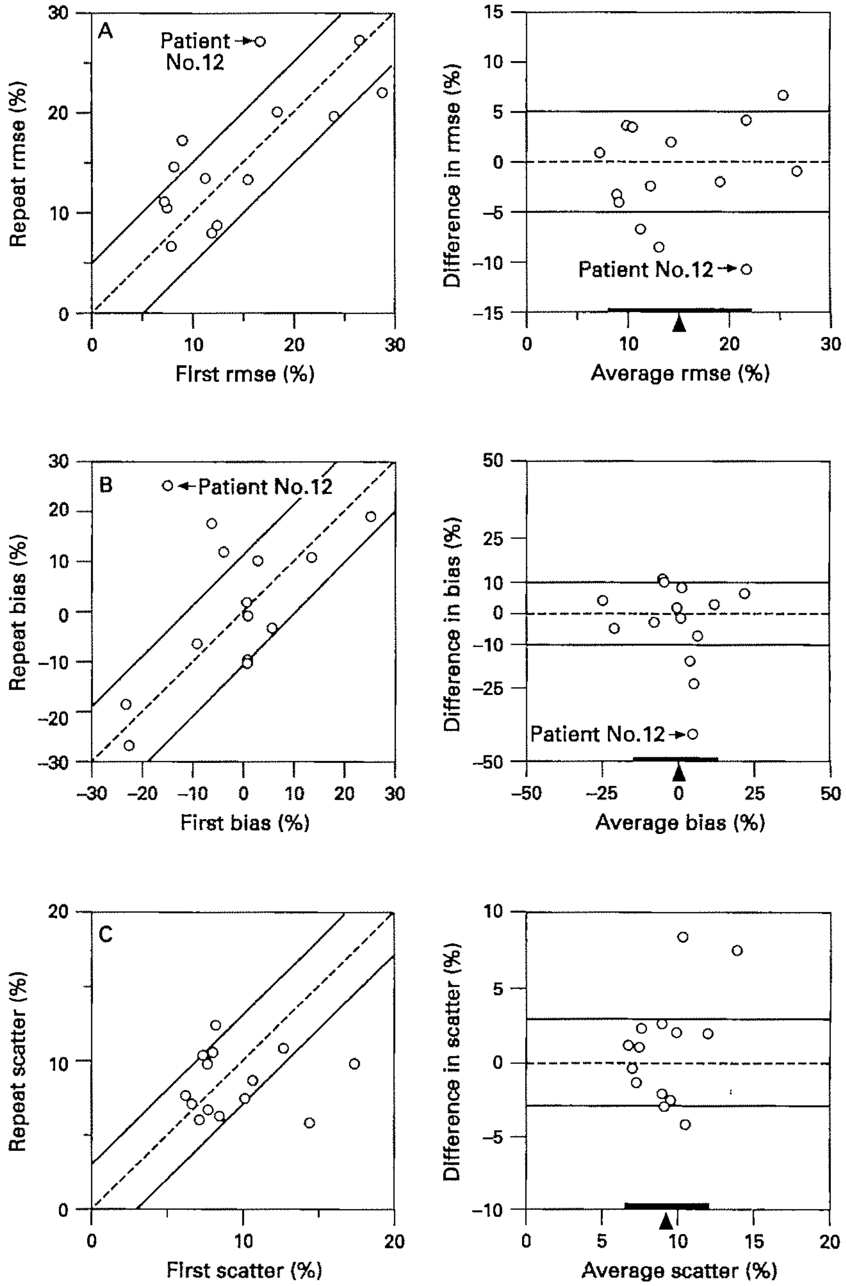

Figure 3 Left: scattergrams of the repeat *vs* first observations on each of the performance measures: A rmse (total error budget); B: bias (systematic component of performance error); and C: scatter (error around the bias). Broken lines=lines of identity, while full lines enclose a zone where the two observations differ by no more than ±5 % for rmse values, ±11% for biases and ±3% for scatters. Right: re-plotted data and lines from the scattergrams on the left, showing the differences between the repeated observations (first−repeat) *vs* the averages per patient for rmse values (A), biases (B) and scatters (C). ▲ and the thick lines on the abscissae represent the overall results: rmse 15 (7) %, bias 0 (14) % and scatter 9 (3) % (grand mean (SD$_T$)).

measurements as there is no relationship between the differences in repeated observations and averaged individual rmse values.

(2) Figure 3B (left) provides the two sets of systematic errors plotted against each other. The difference between the first and repeat bias is not greater than 11% for most patients (three patients are situated out of this zone). The greatest disparity in bias between repeated observations is −15 *vs* 25% (patient No. 12). Again, there is no relationship between the differences in repeated observations and averaged individual biases, as depicted in figure 3B (right).

(3) Figure 3C (left and right) indicates that scatters, although showing agreement to within ±3% for 11 patients, are heavily dispersed in a cloud without a clear link between the repeated observations.

From the right-hand graphs in figure 3 it is apparent that the spread of observations is less in the *Y*-direction than in the *X*-direction in figure 3A (right) and, apart from patient No. 12, also in figure 3B (right) but not in figure 3C (right).

ANALYSIS OF VARIANCE

Table 3 summarizes the key results of the variability in the three predictive performance measures. For rmse, the total variance s^2_T was nearly four-fold the within-patient variance s^2_W; thus s^2_W was much smaller than s^2_B. The ratio SD_T/SD_W was 1.98. For bias, s^2_T was twice as large as s^2_W , s^2_W was similar to s^2_B , and the ratio SD_T/SD_W was 1.39. For scatter, s^2_T was not much different from s^2_W , s^2_W was much larger than s^2_B, and the ratio SD_T/SD_W was 1.05.

Table 3 Variability in the predictive performance measures of the model obtained in 14 patients who received an enflurane anaesthetic twice. s^2_W=within-patient but between repeat anaesthetics (i.e. repeatability) variance, s^2_B=between-patient variance, s^2_T=total (i.e. reproducibility) variance, SD_W=repeatability standard deviation, SD_B=between-patient standard deviation, SD_T=reproducibility standard deviation[7 8]

	Rmse	Bias	Scatter
Minimum (%)	6.73	−26.66	5.89
Maximum (%)	29.07	26.12	17.46
s^2_W (%^{2})	12.80	102.64	6.85
s^2_B (%^{2})	37.45	97.68	0.74
s^2_T (%^{2})	50.24	200.32	7.59
SD_W (%)	3.58	10.13	2.62
SD_B (%)	6.12	9.88	0.86
SD_T (%)	7.09	14.10	2.75

MULTIPLE REGRESSION ANALYSIS

The average of the two repeated measurements obtained per individual, representing the best estimate of a "personal" result for each patient (e.g. a personal rmse or bias), was used to assess the potential influence of anthropometric patient characteristics on an individual's performance measures. Multiple regression analysis failed to detect a relationship between age, sex, body weight, BMI or BSA and the personal predictive performance measures.

Discussion

We have found that there was a link between the first and repeated measurement of the performance of the model. This was so for the measures rmse (total error size) and bias (systematic error), but not for scatter (fig. 3). This finding implies that most patients behaved similarly during both anaesthetics.

RATIONALE FOR A MODEL AND ITS VALIDATION

Our results are part of the necessary validation of a model. System models are used for clinical anaesthetic management, educational applications, research development, and to address economic or ecological issues. A physiological model is useful in a variety of "what happens if" scenarios, for example by predicting the effects of physiological perturbations on drug distribution.[10] Such a model is based on numerous simplifying assumptions, for example average values of physicochemical data and physiological variables are used. The disposition of a drug in any subject, however, is only predictable within limits as a result of variability in pharmacokinetics and pharmacodynamics.[11–15] It is critically important to know the impact of this variability on the imprecision and reliability of model-based predictions because far-reaching conclusions can be drawn from model behaviour. The variability we wished to study was reflected in the variation in the predictive performance measures of the model.

Our overall estimates of the performance measures of the model were in accordance with those found in a former validation study.[3] Standards to judge the validity of a system model for volatile anaesthetics have been defined previously.[4] We focused on the trueness, that is the closeness of agreement between predicted and measured concentrations.[7 16 17] A valid model should not under predict or over predict reality in a systematic way. Although it is reasonable to expect a degree of bias for each patient on each occasion, the group bias should approximate zero. This study yielded a group bias of 0 (14) % (grand mean (SD_T)). In addition, the total error size, assessed in terms of rmse, should be acceptable for most patients. Relying on biological variability in uptake found by several authors, we proposed that the total error size of a physiological model with zero group bias is acceptable if the rmse value of at least 68% of the subjects is <30 %.[4] In this study rmse was <30% for the 28 analysed observations.

EXTENT OF CORRESPONDENCE

It is most unlikely that repeated observations on the same patient would give identical values for each variable (rmse, bias or scatter) in every individual. Figure 3 illustrates the percentage of subjects showing agreement to within selected numbers of units. We used zones around the lines of identity of approximately one-sixth of the full axis range, thus indicating those patients whose repeated results differed little in comparison with the total range of variability between patients. In spite of a total range of 7–29%, the repeat rmse differed by no more than 5% from the first for 10 of 14 patients. The systematic error had a wide range (−27% to +26 %), whereas the difference between the first and repeat bias was not greater than 11% for most patients. If we translate the percentage bias into vol% of end-expired concentration, a difference of less than 11% implies that the systematic errors on the two occasions differed by less than 0.11 vol% for each vol% of anaesthetic. This is a small discrepancy in clinical terms. It appears that individuals who have or have not deviated from an anticipated pharmacological behaviour on one occasion tend to behave alike on an alternate similar occasion. Subjects can deviate, even grossly, from the grand mean, yet exhibit a high level of repeatability (observations in the top right and bottom left of figure 3B) (left). Therefore, model-based predictions have an extra clinical value.

COMPONENTS OF BIOLOGICAL VARIABILITY

We estimated that, although the repeat scatters differed little for most patients (fig. 3), 90% of the total variance resulted from within-patient variance (table 3). As scatter varies much more from one anaesthetic to the next in any one patient than it does between the average scatter for different patients (fig. 3C (right)), it may be that much of this scatter is not caused by variation within the patient but by some other cause.

We estimated for rmse and bias that 75% and 49%, respectively, of the total variance was caused by between-patient variance. In contrast with scatter, the variance in rmse was mainly attributable to systematic differences between patients. For bias, variance was distributed evenly among its two components.

Comparing the results of this study with those of others is difficult because data on recurrent measurements of inhaled anaesthetics are scarce and do not include estimates of both between-patient and within-patient but between repeat anaesthetic variabilities.[18–20] Studies in an other area of clinical research also found that prediction within patients was easier than that between patients when using a physiologically based formula, and that such information can be useful in clinical practice.[21]

ASSOCIATION WITH PATIENT CHARACTERISTICS

The high within-patient consistency was a reason for investigating the possible association of individual results for rmse or bias with age, sex, body weight, BMI or BSA. As in previous studies, a relationship between individual patient characteristics and performance measures could not be established.[2–4] This is not surprising because these data are primary inputs to the model. It uses an individualized input to calculate some physiological variables such as cardiac output and functional residual capacity. The characteristics studied cannot be used to improve the model. Additional, yet unknown, factors may contribute in a significant extent to an individual's pharmacokinetic response. Future research may reveal if our model-based predictions can be scaled further between individuals by other "personal" factors.

Our results ask the question whether we should save patient-related findings in a directly accessible "anaesthetic passport" (bearing the patient's anaesthetic finger printings). This may be an aid to anaesthetists in the future.[22] They may plan the anaesthetic of their patients on the basis of the average behaviour of a standard human, perhaps also according to institutional algorithms. Subsequently they may adapt the anaesthetic drug administration to tailor the anaesthetic to the physiological status of their patient. Models can facilitate these processes of decision making. But anaesthetists are also interested in identifying those patients who are likely to deviate from anticipated average behaviour. Our results suggest that determination of bias (or rmse) in a patient on one occasion, even if that bias is large, may be a useful predictor of bias on subsequent occasions. This is well illustrated in figure 3B (left), apart from patient No. 12. Other authors have shown that the correlation of anaesthetic uptake with easily observable patient characteristics is poor.[18 23] If the patient must receive another anaesthetic, the judicious use of data identified during a former anaesthetic may be the best basis available to adjust the "rules of thumb" which anaesthetists use when managing a patient.[24]

RESERVATIONS

The data showing high repeatability were gathered under similar clinical conditions. Therefore, repeatability values should not be extrapolated to apparently different conditions. Model-based drug regimens and algorithms are not intended as rigid recipes.[18] They offer a reasonable approach to anaesthetic management that must be individualized with the aid of clinical observations and vigilant monitoring of end-tidal concentrations and haemodynamic variables.[25]

A few patients with poor consistency and one outlier were found. Their presence suggests that the use of an adaptive model or feedback-controlled anaesthesia is worth considering for future development.[23 26 27] The control algorithms needed can be developed initially with the aid of a model which should be well validated and exhibit a realistic amount of variability such as that found in the present study.

We believe that repeatability data should be available to each research group studying the predictive performance of models, not only because it is important to separate within-patient from overall variability, but also because poor repeatability may highlight the need to re-examine the various procedures involved in gathering the data.[28]

In this era of multi-gas monitoring techniques and impending automated administration of volatile anaesthetics, there is still a definite role for well validated models of human physiology and pharmacology. The results for overall variability show that a dosing regimen based on our model is a useful starting strategy for administering closed-circuit inhalation anaesthesia; the results for within-patient variability suggest that a patient may benefit from using a starting regimen corrected from the findings obtained during a former anaesthetic.

Appendix 1

A concise non-mathematical account of the model is presented here. A comprehensive quantification and mathematical formulation have been presented elsewhere.[1] Our physiological model depicts the body and closed anaesthetic circuit as a system of 14 compartments (fig. 4). A liquid anaesthetic agent injected directly into the closed system is assumed to mix uniformly after vaporization with the contents of the closed breathing system. The anaesthetic agent is taken up from the alveolar space and distributed to the other tissue compartments: heart, brain, kidneys, liver (including all other well-perfused organs), muscles, connective tissue and adipose tissue. The model derives from the subject's age, sex, body weight and height, the other physiological variables, including deadspace, alveolar space, blood volume, cardiac output and tissue volumes.

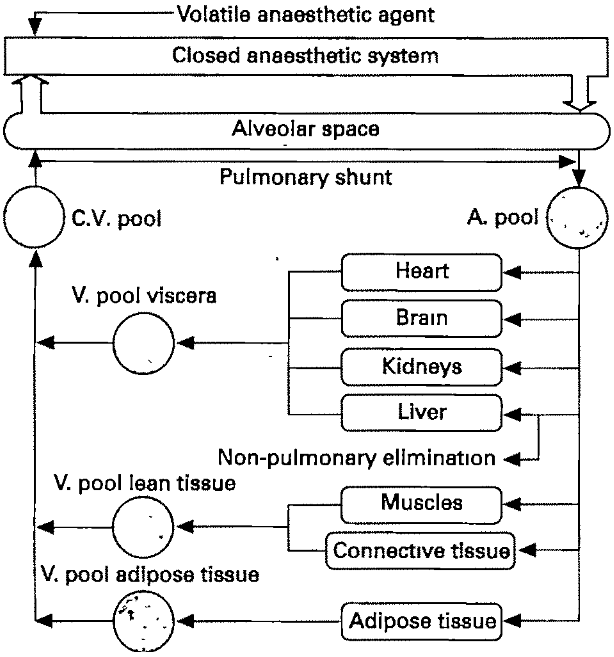

Figure 4 Simplified schematic diagram of the 14-compartment physiological model which includes the closed anaesthetic circuit and the patient tissues; the circles represent the blood pools (A.=arterial; (C.) V.=(central) venous).

Our system model differs from previous models for closed-circuit anaesthesia in four main ways. (1) Unlike the model of Lowe and Ernst it does not assume that the arterial concentration remains constant.[29] This implies that the model is able to predict breath-by-breath end-expired concentrations after bolus injections of a liquid anaesthetic agent into the closed system. (2) Our model does not assume that either the circulating times are zero or that venous blood is part of each tissue compartment. Rather we followed Mapleson's suggestions by introducing his concept of blood pools that mimics circulation times in the body.[30] (3) The model incorporates a non-pulmonary route of elimination for enflurane and halothane.[3 4] (4) Age-related blood-gas and tissue–blood partition coefficients can be introduced. For halothane we showed that this improved the accuracy of the model.[4]

Appendix 2

Suppose we have p patients called i ($i=1, 2, \ldots, p$) with m repeated observations on the same patient, giving a total of pm results for each of the three performance measures. If any one of these results is y_{ik} ($k=1, 2, \ldots, m$), then the individual mean result for patient i is:

$$\bar{y}_i=\frac{1}{m}\sum_{k=1}^{m} y_{ik}$$

The individual SD, that is a measure of the dispersion of the m repeated observations on the same subject, is given as:

$$s_i=\sqrt{\frac{1}{m-1}\sum_{k=1}^{m}(y_{ik}-\bar{y}_i)^2}$$

The grand mean for the sample population is:

$$\bar{Y}=\frac{1}{\mathrm{p}}\sum_{i=1}^{\mathrm{p}}\bar{y}_i$$

Three variances are calculated for each of the performance measures.

(1) Within-patient (or repeatability) variance s^2_{W} is the average of individual variances:

$$s^2_{\mathrm{W}}=\frac{1}{\mathrm{p}}\sum_{i=1}^{\mathrm{p}} s^2_i$$

(2) Between-patient variance s^2_{B} is an indicator of the variation in expected means between patients; this estimate is based on the distribution of patient means:

$$s^2_{\mathrm{B}}=\frac{1}{\mathrm{p}-1}\sum_{i=1}^{\mathrm{p}}(\bar{y}_i-\bar{Y})^2-\frac{s^2_{\mathrm{W}}}{m}$$

(3) Total sample population (or reproducibility) variance s^2_{T} combines within- and between-patient variances:

$$s^2_{\mathrm{T}}=s^2_{\mathrm{W}}+s^2_{\mathrm{B}}$$

The repeatability and reproducibility SD values are given by $\mathrm{SD_W}=\sqrt{s^2_{\mathrm{W}}}$ and $\mathrm{SD_T}=\sqrt{s^2_{\mathrm{T}}}$, respectively.

Acknowledgements

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A physiological model of induction of anaesthesia with propofol in sheep. 1. Structure and estimation of variables

R. N. UPTON AND G. L. LUDBROOK

Summary

We describe a six-compartment physiological model of the kinetics and dynamics of induction of anaesthesia with propofol in sheep. It includes a faithful description of initial bolus kinetics caused by accurate representations of the inter-relationships between initial vascular mixing, lung kinetics and cardiac output, the use of the brain as the target organ for propofol anaesthesia (two-compartment sub-model with slight membrane limitation), a description of the effects of propofol-induced changes in cerebral blood flow and a combined description of systemic kinetics as two tissue pools. Variables for the model were estimated from an extensive *in vivo* data set using hybrid modelling. Propofol was characterized by rapid transit through the lungs, but a slower transit time though the brain, leading to significant delay between arterial blood concentrations and cerebral effects. (*Br. J. Anaesth.* 1997; **79**: 497–504).

Key words

Anaesthetics i.v., propofol. Anaesthetic techniques, induction. Induction, anaesthesia. Pharmacokinetics, propofol. Pharmacodynamics. Model, physiological. Sheep.

The pharmacokinetics and pharmacodynamics of propofol have been studied widely as a tool for increasing insight into its clinical use. The majority of studies have focused on measurements of the time course of the concentration of propofol in blood, and various measures of cerebral pharmacodynamic effects, including changes in the EEG and clinical indicators of depth of anaesthesia.[1–4] The resulting models of this process have been based typically on a two-, or more commonly, three-compartment systemic model with or without an effect compartment.[5 6]

While this approach can provide useful information, particularly with respect to targeting blood concentrations[6 7] for longer term administration by infusion, the limitations of this compartmental approach for bolus kinetics (or for rapid changes in infusion rate) have been well documented in the pharmacokinetic literature.[8–12] With respect to induction agents, these models fail to describe vascular mixing,[13 14] lung kinetics[8 15] and cerebral drug kinetics[16] in the vital period immediately after bolus injection.[17] Furthermore, these models are not suitable for describing the influence of the common physiological and pathophysiological conditions encountered in surgical patients.

These problems can be attributed to the lack of a physiological basis for these conventional compartmental models. Indeed, it has been shown that adding physiological descriptions of vascular mixing and lung kinetics improves their ability to describe initial bolus kinetics.[18 19] In our laboratory we have recently proposed a model of the first-pass passage of lignocaine from its venous injection site to one of its target organs for toxic effects—the heart.[20] This model embraced the importance of vascular mixing and lung kinetics, but also proposed a physiological site for drug action. Importantly, every aspect of this model was validated extensively using hybrid modelling techniques against an *in vivo* data set rather than arterial blood concentrations alone.

In this article, we extend this model to produce a physiologically realistic model of the kinetics and dynamics of induction of anaesthesia with propofol. The model is validated by comparison with recent experimental work from our laboratory using a chronically instrumented sheep preparation with which we have measured arterial and sagittal sinus (effluent blood from the brain) drug concentrations[21] simultaneously with measurements of cerebral blood flow[22] and an index of anaesthetic effects.[23 24] The essential structure of the model is sufficiently general in its form that it can be used to provide qualitative insights into induction of anaesthesia with propofol. Consequently, in this article the model is described and validated. In an accompanying article, the properties of the model and determinants of the induction process are examined in detail.

Methods and results

STRUCTURE OF THE MODEL

An overview of the structure of the model is presented first. It is similar to that proposed

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R. N UPTON, BSC, PHD, G. L. LUDBROOK, MB, BS, FANZCA, Department of Anaesthesia and Intensive Care, Royal Adelaide Hospital, University of Adelaide, North Terrace, Adelaide, SA 5005, Australia. Accepted for publication: April 25, 1997.

Correspondence to R N U.

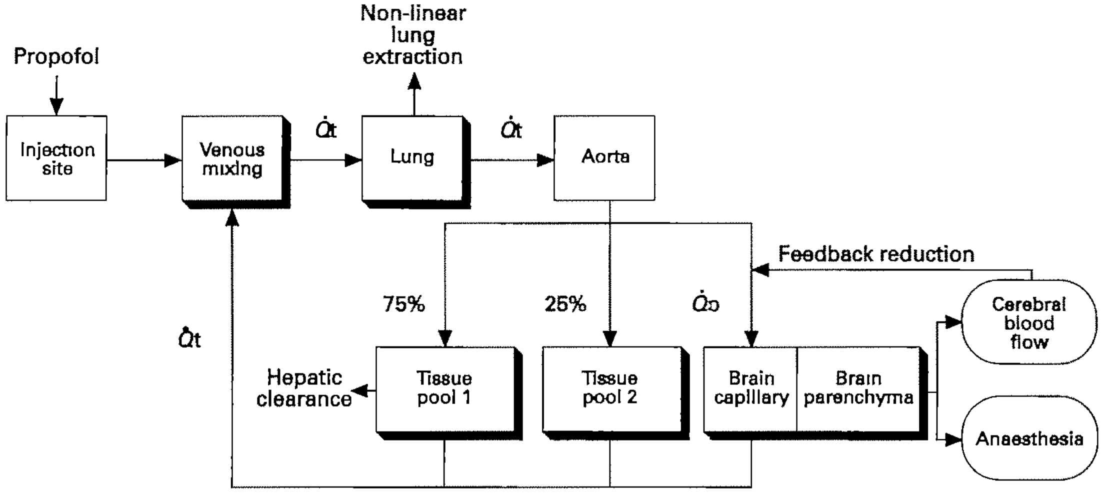

Figure 1 An overview of the model. The model is composed of six compartments (indicated as boxes with shadows) arranged in series and parallel in a circuit through which cardiac output ($\dot{Q}t$) flows. The effects of propofol on cerebral blood flow ($\dot{Q}b$) and depth of anaesthesia are related linearly to its concentration in the parenchymal compartment of the brain, but with a maximum reduction in cerebral blood flow of 50% of baseline. Propofol is removed by non-linear lung extraction and hepatic clearance.

previously,[20] with the addition of recirculation. The justification of this structure will be apparent when the variables of the model are validated subsequently against the *in vivo* experimental data.

The model is composed of six compartments in series and parallel (fig. 1). Consider the case where propofol is injected at a constant rate over a period T (e.g. 20 s) into the peripheral venous circulation to produce a square wave concentration peak of duration T. This "slug" of propofol (after Crawford[25]) travels in venous blood towards the lungs. The shape of this slug in the pulmonary artery is independent of the location of the injection site, and is determined in two steps in the model. First, the height of the square wave is adjusted for dilution with the remainder of cardiac output, with the new height given by the dose rate over cardiac output. This accounts for the basic indicator dilution aspect of the injection.[14 26] Second, dispersion of the peak because of intravascular mixing in transit from the injection site to the pulmonary artery is accounted for empirically by the passage of this peak through a small hypothetical well-stirred venous mixing compartment.

The peak then passes through the lungs where it is subject to distribution (described by a well-stirred compartment through which cardiac output flows) and a non-linear extraction term caused by metabolism. Emerging from the lungs in arterial blood, the peak is distributed to the remaining organs of the body. The brain was of special interest as the target organ for anaesthesia with propofol[21]—the kinetics were represented by a two-compartment model. The first compartment (nominally including capillary blood) was flow-limited, with slight membrane limitation in transfer to the second compartment (nominally including the parenchyma). The resultant sub-model of the brain has characteristics of both flow and membrane limitation,[27] and was modified further by a feedback loop accounting for propofol-induced reductions in cerebral blood flow. The maximum reduction in cerebral blood flow was set at 50% of baseline. The cerebral dynamic effects of propofol—its anaesthetic effects and ability to reduce cerebral metabolic rate and therefore cerebral blood flow—were related linearly to the concentration of propofol in the second compartment of the brain.

The kinetics of propofol in the remainder of the body were of interest to account for the effects of recirculation only, and the remainder of the body was therefore grouped together as compartments representing two tissue pools. The first was nominally the well-perfused organs, such as the liver and kidneys, received 75% of cardiac output (less cerebral blood flow) and included a first-order elimination process that represented hepatic clearance. The second received the remainder of the cardiac output and was nominally the poorly perfused tissues, such as muscle and fat. To complete the model, recirculated drug emerging from the brain and the tissue pools was returned to the venous circulation.

EQUATION SOLVING

The model was implemented as a set of differential equations (appendix 1) and was solved using the "Scientist" modelling package (Scientist for Windows, Version 2, Micromath, Salt Lake City, UT, USA), although any differential equation solver would be suitable. In general terms, the model could be used to predict the effect of propofol with respect to depth of anaesthesia and reductions in cerebral blood flow, and its concentrations in the brain parenchyma, pulmonary artery, aorta and sagittal sinus (venous effluent from the brain).

VARIABLE ESTIMATION

A shortcoming of many physiological models in the past has been the lack of a detailed *in vivo* experimental data set of simultaneously measured regional drug concentrations *and* blood flows with which to estimate the variables of the model. Our *in vivo* data set[21 24] allowed the use of hybrid physiological modelling[28 29] to estimate the variables of the model. The process used has been reported in detail previously,[20] but in general terms each component of the model (e.g. each compartment in fig. 1) is compared independently with the appropriate component of the data set. Input into each component is described by a series of empirical forcing functions that closely match the measured data, while the variables of the sub-model representing that component are determined by least squares fitting of the measured output data. For example, to model cerebral kinetics, arterial blood concentrations and cerebral blood flow (input to the brain) are fitted to empirical forcing functions. The variables of the chosen model of the brain (such as apparent volume of the brain) are then estimated by least squares curve-fitting by comparing the predicted and measured sagittal sinus concentrations (output of the brain). In this manner, the variables of large models can be estimated with a high degree of confidence independently of other aspects of the model. Detailed estimation of the variables is described below. The symbols and equations used are summarized in tables 1 and 2, and appendix 1.

Curve-fitting using a least squares algorithm was performed using the "Scientist" modelling package; the best fit was judged by maximization of the "model selection criteria (MSC)" of this package, which is the Akaike Information Criterion scaled to normalize for data sets of different magnitudes.[30] The higher the value of the MSC, the better the fit. The goodness of fit of individual data sets was also reported as an r^2 value.

Table 1 Variables of the model

Variable	Description
t	Time
C_{pa}	Pulmonary artery concentration
C_{art}	Arterial concentration
C_{ss}	Sagittal sinus concentration
C_{bp}	Brain parenchyma concentration
$\dot{Q}_{red}$	Percentage reduction in cerebral blood flow
A_{inc}	Percentage increase in "anaesthesia"

Venous mixing (lines 22–23 of appendix 1)

The fundamental indicator dilution basis of venous mixing is central to indicator methods for measuring cardiac output[26] and has been confirmed experimentally in the context of bolus injection.[14] However, dispersion of the peak in transit from the venous injection site to the pulmonary artery is a complex process.[31] An empirical but accurate method of accounting for dispersion with a small venous mixing compartment has been validated previously in our preparation.[20] The volume of the mixing compartment was shown to be 0.255 litre, and cardiac output itself has been measured repeatedly in our preparation—the baseline value was set at 5.6 litre min^{-1}.[32] This baseline value was used for simulation of "normal" data sets; in reality it should be acknowledged that there is sheep-to-sheep and day-to-day variation in cardiac output.[33]

Lung kinetics (lines 26–28 of appendix 1)

We have reported previously that the initial arterial concentrations of propofol after bolus injection were non-linear at low doses[21] and attributed this to non-linear extraction across the lung. The work of Mather and colleagues,[34] also using sheep, provided more information on this process. They showed that extraction occurred after prolonged infusions, and was therefore likely to be a result of metabolism (or essentially irreversible distribution). Re-analysis of their data showed that this metabolism was greatest at low concentrations and appeared to become saturated at higher concentrations (extraction of 68% at a steady state pulmonary artery concentration of 0.65 mg $litre^{-1}$, 26% at 3.4 mg $litre^{-1}$ and 15% at 8.35 mg $litre^{-1}$, respectively). It was found that the relationship between the inverse of extraction ($1/E_{lung}$) and the afferent pulmonary artery concentration (C_{pa}) could be described by the following equation (r^2=0.987; fig. 2):

$$\frac{1}{E_{lung}}=0.007C_{pa}+0.013 \qquad (1)$$

The remaining task was to estimate the

Table 2 Variables of the model for propofol in sheep

Variable	Description	Value used	Source
Dose	Total dose	200 mg	Default only
T	Duration of injection	20 s	Default only
$\dot{Q}t$	Cardiac output	5.6 litre min^{-1}	Measured / hybrid modelling
V_{mix}	Volume of the hypothetical venous mixing compartment	0.255 litre	Hybrid modelling
V_{lung}	Apparent volume of the lung	3.607 litre	Hybrid modelling
E_{lung}	Extraction by the lung	see equation (1)	Measured by Mather and colleagues[34]
V_{bc}	Apparent volume of brain capillary space	0.143±0.011 litre	Hybrid modelling
V_{bp}	Apparent volume of the brain parenchyma	0.035±0.009 litre	Hybrid modelling
PS	Membrane permeability of the brain	0.032±0.009 litre min^{-1}	Hybrid modelling
$\dot{Q}bb$	Baseline cerebral blood flow	0.04 litre min^{-1}	Measured
$\dot{Q}max$	Maximum reduction in cerebral blood flow	50%	Assumed
S_Q	Slope of linear pharmacodynamic model for cerebral blood flow	19.82±1.34	Hybrid modelling
S_A	Slope of linear pharmacodynamic model for anaesthesia	85±3	Hybrid modelling
V_1	Volume of tissue pool 1	15.67±2.95 litre	Hybrid modelling
V_2	Volume of tissue pool 2	570±131 litre	Hybrid modelling
F	Fraction of cardiac output going to V1	0.75	Assumed
Cl_{hep}	Hepatic clearance	1.12±0.25 litre min^{-1}	Measured by Mather and colleagues[34]

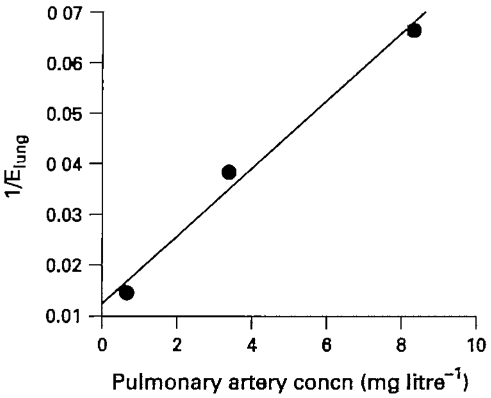

Figure 2 Steady state lung extraction (E_{lung}) of propofol against pulmonary artery concentration, re-analysed from the data of Mather and colleagues.[34] The r^2 value of the linear regression was 0.987.

distribution volume of the lung while taking into account this extraction (although it is relatively low at anaesthetic concentrations of propofol). Data for this purpose were the previously published initial increase in arterial concentrations of propofol measured during a 2-min infusion of propofol at a rate of 50 mg min^{-1}.[21] The time course of these arterial concentrations depends on two factors. First, in the absence of recirculation, concentrations increase to a steady-state value that depends only on the dose rate, cardiac output[14] and magnitude of the extraction process described by equation (1). The rate that they reach this value depends only on the magnitude of vascular mixing and the distribution of propofol in the lungs.

Hybrid modelling of the vascular mixing and lung kinetics subsystems, with dose as the input and arterial concentration as the output, was used to estimate the unknown variables of this sub-model—cardiac output (as it was not measured in this series of studies) and distribution kinetics in the lung. Measurement of cardiac output in this way is analogous to its measurement using indicator dilution principles.[26] Only data for the first 2 min of the infusion were used to ensure the measured concentrations were not distorted by recirculation, which is insignificant in this period.[20] In accord with our previous model, the lung distribution kinetics were represented initially as a single compartment through which cardiac output flowed.[20]

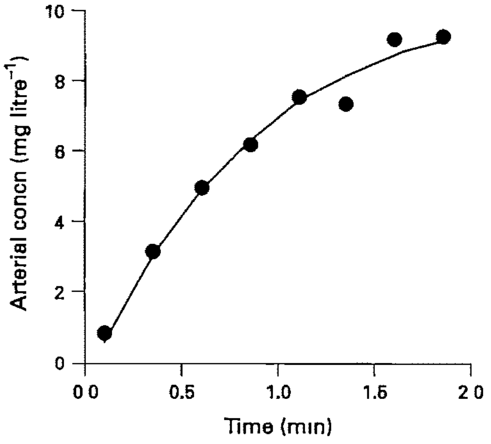

Figure 3 Measured (●) and fitted (line) arterial propofol concentrations used to estimate apparent volume of the lung.

It was found that this simple model allowed unique estimates of both cardiac output (mean 4.26 (SD 0.25) litre min^{-1} for these studies) and the apparent volume of the lung (mean 3.61 (SD 0.30) litre), and accurately described the measured data (r^2=0.997; MSC=3.62) (fig. 3). This equates to relatively rapid transit of propofol through the lung, with a mean transit time of 0.85 min. For comparison, the mean transit time of the vascular mixing process was 0.06 min.

Cerebral kinetics and dynamics (lines 31–38 of appendix 1)

The models of cerebral kinetics and dynamics were developed concurrently in order to account for the following observations, and were compared with the previously published studies of the cerebral kinetic and dynamics of propofol after a dose of 100 mg infused over 2 min.[21 24]

Relationships between propofol concentrations and cerebral blood flow. The pharmacokinetic modelling of anaesthetic agents is complicated as the majority of agents affect cerebral blood flow.[21 35] It was felt that the model should account for our previous observation that propofol reduced cerebral blood flow commensurate with reductions in cerebral metabolism.[24] The time course of these reductions was found to correlate linearly with the time course of mean brain concentrations of propofol (calculated using mass balance principles) but were delayed relative to the time course of arterial or effluent brain concentrations.[21] Baseline cerebral blood flow in the model was also set at 40 ml min^{-1} in accord with our previous observations.[22] The model should also be compatible with the observation that most anaesthetics can reduce cerebral blood flow only to a minimum of approximately 50% of baseline, consistent with abolishing synaptic function but not cellular respiration.[36]

Unpublished data from our laboratory have shown that propofol has minimal effect on cardiac output in sheep for bolus doses of up to 200 mg, in agreement with a report of a minor effect of propofol on cardiac output at "normal" blood concentrations in open chested pigs.[37] Therefore, the effects of propofol on cardiac output were not incorporated into the model.

Relationships between propofol concentrations and the depth of anaesthesia. To quantitate the time course of depth of anaesthesia after propofol administration in our preparation, we developed previously an algesimetry method based on the subcutaneous electrical current required to make a sheep withdraw its leg,[23] a concept similar to that used in the determination of minimum alveolar concentration (MAC) for volatile anaesthetic agents. While this method is restricted to measuring light planes of anaesthesia, it was found that this index correlated linearly with the time course of mean brain concentrations of propofol calculated using mass balance principles,[21] but again was delayed relative to arterial or sagittal sinus concentrations. The implication of these observations is that both this measure and other more traditional indicators of depth of anaesthesia, such as loss of consciousness and eyelash reflex, can be placed on the line of increasing brain concentrations thereby negating the temporal aspects of drug delivery to the brain.

The cerebral pharmacokinetic–pharmacodynamic model. Initial studies compared cerebral kinetics (as given by sagittal sinus concentrations and cerebral blood flow) with a single flow-limited compartment, and a membrane-limited two-compartment model, as used previously for thiopentone in this preparation.[16] Both were good descriptions of the data, with a slight statistical preference for the membrane-limited (r^2=0.995; MSC=4.91) over the flow-limited (r^2=0.992; MSC=4.55) model. However, the flow-limited compartment model was excluded further as this requires that mean brain concentrations and effluent sagittal sinus concentrations are proportional, and are delayed to equal extents relative to the cerebral effects. This is at odds with the two observations discussed in the previous section.

A property of the membrane-limited model is that sagittal sinus concentrations cannot be used to provide precise information on concentrations in the second compartment of the brain. This information was provided by allowing these concentrations to be related to the dynamic effects of propofol (both cerebral blood flow and depth of anaesthesia). Initially, more complex E_{max} and sigmoid E_{max} dynamic models[38] were examined, but it was found that the most appropriate model (i.e. highest value of r^2 and MSC together with precise estimates of variables) was one in which the concentration–effect relationships were linear with intercepts of zero, and the volume of the first compartment was set at the value determined for the kinetic data alone. An upper limit of 50% for reduction in cerebral blood flow was used, as discussed previously, on theoretical grounds only.

The resultant cerebral kinetic–dynamic model was a simple, yet elegant, description of the measured data, requiring estimation of only four variables (V_b, PS, S_Q, S_A) from three concurrent data sets (sagittal sinus concentrations, cerebral blood flow, depth of anaesthesia). Estimates of the variable values were precise (table 2). The kinetic component of the model was a good description of sagittal sinus concentrations (r^2=0.948; fig. 4), and the ratio of membrane permeability (PS) over flow of 0.8, places the model in the category of those that are both flow and membrane limited.[39] The dynamic components of the model were also good descriptions of the data (fig. 4) with r^2 values of 0.964 and 0.983 for blood flow and depth of anaesthesia, respectively. The overall MSC value for the combined kinetic–dynamic model was 3.77, and the respective r^2 values listed above show that approximately 95% of the variability in all three data sets could be accounted for by the model.

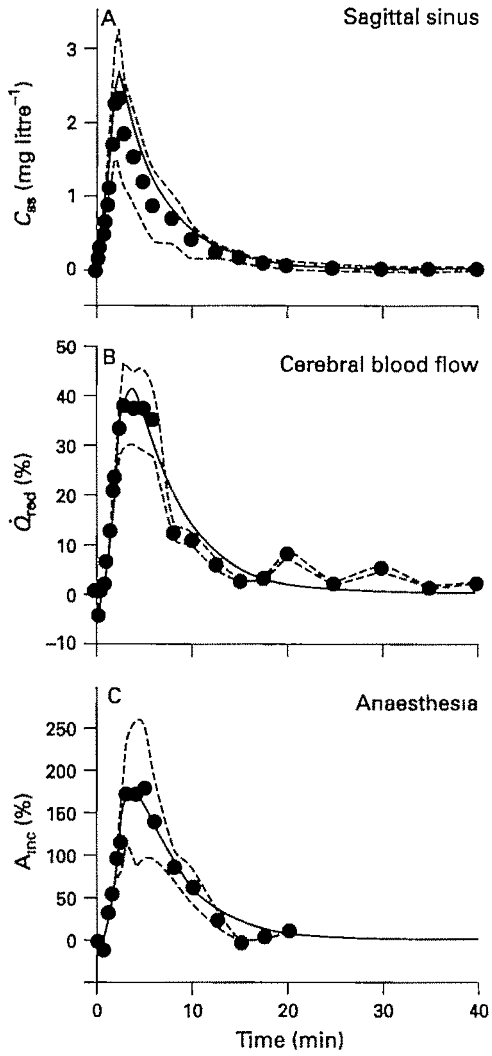

Figure 4 Measured data and best fit of the combined cerebral kinetic–dynamic model. A: Measured sagittal sinus concentrations (●) (broken lines=upper and lower 95% confidence limits) for propofol 100 mg infused over 2 min, together with the fitted concentrations (solid line). B: Equivalent data for measured cerebral blood flow expressed as percent reduction from baseline ($\dot{Q}_{red}$). Note that the model does not predict transient reductions in flow often measured after emergence from anaesthesia between 20 and 30 min.
C: Equivalent data for depth of anaesthesia (as given by the current required for leg withdrawal) expressed as a percentage increase from baseline (A_{inc}). Note that the experimental measurements were stopped at 20 min when baseline had been re-established.

Systemic kinetics (lines 45–46 of appendix 1)

The systemic kinetic variables of the model were estimated from pilot data from our sheep preparation describing arterial concentrations of propofol during and after a 45-min infusion of propofol at a rate of 10 mg min^{-1} (n=3 sheep). It was felt that two tissue pools were appropriate for systemic kinetics, the second pool accounting for the widely acknowledged "deep" distribution of propofol.[5] These pools received fixed fractions of 75% and 25%, respectively, of cardiac output (less cerebral blood flow). Initial studies showed that the model was under-determined if clearance, as a result of elimination and deep distribution kinetics, was estimated simultaneously, which is consistent with our previous work showing that these processes are indistinguishable, even at steady state, in some circumstances.[40] Fortunately, Mather and colleagues[34] made direct measurements of propofol

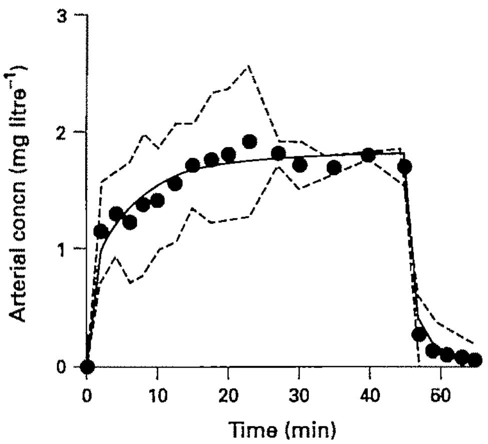

Figure 5 Measured arterial propofol concentrations (●) (broken lines=upper and lower 95% confidence limits) used to estimate systemic kinetic variables cardiac output and the volumes of tissue pools 1 and 2, and the best fit of the model (solid line).

organ clearance in sheep, and found that with the exception of pulmonary extraction accounted for above, clearance was predominantly hepatic and was relatively constant (1.13 (SD 0.25) litre min^{-1}) with almost complete extraction of propofol by the liver. Consequently, clearance from tissue pool 1 was set at this value. The unknowns to be determined from the 45-min infusion data were therefore cardiac output and the volume of tissue pools 1 and 2. These were estimated with an adequate degree of confidence from the data (6.41 (SD 0.1) litre min^{-1}, 15.7 (2.9) litre, 570 (131) litre, respectively), and were a good fit of the measured data ($r^2=0.995$; MSC=3.75) (fig. 5).

COMPARISON WITH INDEPENDENT DATA SET

The good fits of the data shown in figures 2–5 illustrate that the structure of the sub-models used were appropriate descriptions of the relevant data sets. To examine the overall integrity of the completed model, it was used *de novo* to predict a set of data that could be compared with an independent data set not used in the validation steps of the model. The data set chosen was pilot data ($n=3$) of sagittal sinus concentrations of propofol after a 45-min infusion at a rate of 10 mg min^{-1}. There was good agreement between simulated and measured concentrations (fig. 6), thereby showing that the model is capable of accurate *de novo* predictions.

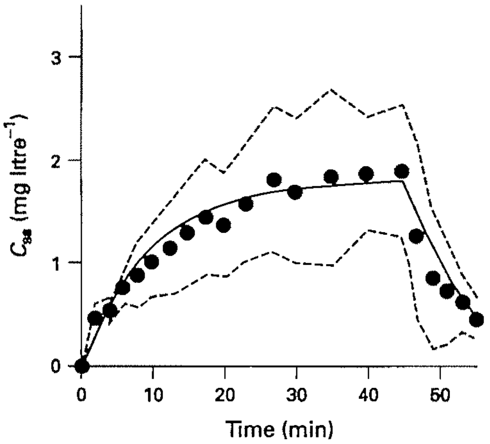

Figure 6 Estimated variables (table 2) were used with the model to simulate sagittal sinus concentrations resulting after an infusion of propofol 10 mg min^{-1} for 45 min. These were compared with an independent data set (i.e. data not used to validate the model) consisting of measured concentrations from a pilot study ($n=3$). There was good agreement between simulated (solid line) and measured (●) data (broken lines= upper and lower 95% confidence limits).

Discussion

For describing bolus kinetics, traditional compartmental pharmacokinetic models invariably feature a central compartment to which drug is added instantaneously or as a very short infusion. A common problem has been highly variable estimates of this central volume, which appears to relate to the time[9] and site[2] of the first blood sample, and the physiological state of the patient. Two important points arise from this article. First, together with the work of others,[18 19] it has shown that in physiological terms the central compartment is in fact a poor representation of the interactions between vascular mixing, lung kinetics and cardiac output, and that taking these factors into account can greatly improve the description of bolus kinetics. Second, the initial concentrations in the central compartment are poorly related to the important cerebral effects of propofol, and these are described better by using the brain as the target organ for these effects.

A drawback of the increased complexity of our model is the non-intuitive nature of the interactions between the various components, but this can be addressed by using a working version of the model to simulate various data sets.[41] Importantly, this increased complexity allows determinants of the onset of anaesthesia to be described by variables directly relevant to the practice of anaesthesia (e.g. cardiac output and cerebral blood flow), which are examined in more detail in an accompanying article.[41] A traditional problem of physiological models, that of estimating large numbers of variables from an under determined data set,[29] has been circumvented by hybrid modelling of *in vivo* data such that all variables were estimated confidently and essentially independently of each other.

The limitations of the present model are in addition to those discussed for the previous model of first-pass concentrations,[20] but in general amount to "fine tuning" of the model rather than structural flaws. These include the fact that it is based on animal data (discussed in more detail in our accompanying article[41]), does not account for lag during passage through blood vessels (insignificant when drug transit times through organs are high relative to vascular transit times), has a poor description of injection site concentrations (not of direct clinical relevance) and does not account for protein binding (can be ignored in individuals if binding is linear and protein concentrations are constant after injection) or tachyphylaxis (overall role uncertain). It should also be remembered that the model does not account for the haemodynamic effects of propofol, which may significantly influence its use, nor does it account for blood flow changes secondary to respiratory depression in unventilated animals.

The present model (and data upon which it is based) has several implications for other models of propofol kinetics. First, the model incorporates two sources of non-linearity: drug-induced cerebral blood flow changes and concentration-dependent lung extraction. Therefore, models that are entirely linear in their structure are likely to be in error when predicting the outcome of large changes in dose. Second, the model provides some insight into the nature of the commonly used effect compartment rate constant k_{e0}, relating blood concentration (usually arterial) to a measured effect.[42 43] In the case of propofol, our study revealed k_{e0} to be a composite of flow and permeability terms describing entry of propofol into brain tissue and, for the reasons described above, would not have the properties of linearity and first-order kinetics usually ascribed to k_{e0}. However, rough calculations show that the effect delay predicted by this model could be approximated by an effect half-life relative to arterial blood that ranged from 3.5 to 7 min. The slight membrane limitation in the model of the cerebral kinetics of propofol is supported by recent data in human.[44]

In summary, we propose that the model provides useful insight into which kinetic and dynamic processes contribute to the onset and offset of anaesthesia with propofol.

Appendix 1

EQUATIONS DESCRIBING THE MODEL

The equations of the model, written in a form suitable for the differential equation solver and modelling environment "Scientist" (Scientist for Windows, Version 2, Micromath, Salt Lake City, UT, USA). The conventions used are common to many programming languages, but note that an apostrophe after a variable indicates a differential with respect to time (thus C' is dC/dt) and that the "pulse" function is used to generate a square wave input. Annotations are preceded by "//", and symbols are explained in detail in tables 1 and 2. The line numbers on the right are for reference purposes only. In this example, 200 mg is administered over 30 s.

```
// A physiological model of the kinetics and dynamics of induction
   of anaesthesia with propofol in sheep

IndVars: t
DepVars: Cpa, Cart, Css, Cbp, Qred, Ainc

Params: Qt, Vmix, Vlung, Vbc, Vbp, PS, Qbb, SQ, SA, V1, V2,
   F, CLhep

//Dose—provision for 2 square wave injections
   dose1=200
   start1=0
   bigT1=0.5
   doserate1=pulse(dose1,start1, bigT1)

   dose2=0
   start2=0
   bigT2=0
   doserate2=pulse(dose2,start2, bigT2)

doserate=doserate1+doserate2

//Venous mixing compartment, including addition of recirculation
   Cinj=doserate/Qt
   Vmix*Cpa'=Qt*(Cinj-Cpa)+Q1*C1+Q2*C2+Qbrain*Css

//Lung kinetics
Carttemp'=Qt/Vlung*(Cpa-Carttemp)
Elung=1/(0.006623*Cpa+0.01257)
Cart=Carttemp*((100-Elung)/100)

//Combined brain kinetic and dynamic model including drug-
   induced cerebral blood flow changes
Qredtemp=SQ*Cbp
Ainc=SA*Cbp

Qmax=50
Qred=IFGTZERO((Qredtemp-Qmax),Qmax,Qredtemp)
Qbrain=Qbb*((100-Qred)/100)
Vbc*Css'= Qbrain*(Cart - Css)+PS*(Cbp - Css)
Vbp*Cbp'=PS*(Css-Cbp)

//Tissue pool blood flows
Q1=(Qt-Qbrain)*F
Q2=(Qt-Qbrain)*(1-F)

//Tissue pool kinetics
   V1*C1'=Q1*Cart - Q1*C1 - CLhep*C1
   V2*C2'=Q2*Cart-Q2*C2

// Parameter values for PROPOFOL
//Units are mg, litre, min
Qt=5.6
Vmix=0.255
Vlung=3.607
Vbc=0.143
Vbp=0.035
PS=0.032
Qbb=0.04
SQ=19.82
SA=85
V1=15.67
V2 =570
F=0.75
CLhep=1.12

// Initial conditions for numerical integration
t=0
Cpa=0
Carttemp=0
Css=0
Cbp=0
C1=0
C2=0
***
```

Acknowledgements

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A physiological model of induction of anaesthesia with propofol in sheep. 2. Model analysis and implications for dose requirements

G. L. LUDBROOK AND R. N. UPTON

Summary

The determinants of induction of anaesthesia with propofol, and their implications for dose requirements, were analysed using a physiological model of the process, validated previously using sheep data. The maximum depth of anaesthesia occurred 2–3 min after cessation of injection. Injection over 2 min minimized the induction dose. More rapid injection (<1 min) did not significantly hasten induction, but increased dose requirements and produced large peak arterial concentrations, potentially risking increased hypotension. Cardiac output and cerebral blood flow were important determinants of the induction process. Increased cardiac output decreased the duration of anaesthesia, while increased cerebral blood flow increased the depth but not duration of anaesthesia. The influence on dose requirements of propofol of factors such as anxiety, hyperventilation, age and co-induction with other drugs may be interpreted in terms of their effect on cardiac output and cerebral blood flow. (*Br. J. Anaesth.* 1997; **79**: 505–513).

Key words
Anaesthetics i.v., propofol. Anaesthetic techniques, induction. Induction, anaesthesia. Pharmacokinetics, propofol. Pharmacodynamics Model, physiological. Sheep.

In an accompanying article,[1] we described and validated a physiological model of the kinetics and dynamics of induction of anaesthesia with propofol in sheep. In brief, the model included a small vascular mixing compartment, a lung compartment with non-linear extraction, the brain represented as a two-compartment model with slight membrane limitation (cerebral effects, including feedback reduction in cerebral blood flow were related linearly to propofol concentrations in the second compartment of the brain), and two compartments nominally representing moderately and poorly perfused tissues, respectively. First-order hepatic clearance was included in the moderately perfused tissue pool. Each component of the model was validated[1] against an extensive previously published *in vivo* data set collected in instrumented sheep,[2–4] such that the model was shown to be capable of accurate *de novo* predictions.[1]

In this companion article, we analyse the structure of the model in order to illustrate its fundamental properties and its implications for dose requirements of propofol in various circumstances. The properties of models of this complexity which represent convoluted physiological systems are not intuitively obvious, but become apparent by systematically examining the influence of each component or variables of the model.

Methods

The detailed structure of the model and estimation of its variables have been published previously.[1 5] The predictions of the model were examined by simulation of a variety of physiological states and dose regimens (elaborated below). The results of simulations were summarized by their influence on the time and magnitude of peak propofol concentrations in arterial blood and brain. The dynamic outcome was summarized by their effect on duration and depth of anaesthesia. We have shown previously that brain concentrations of propofol were related linearly to its major cerebral dynamic effects—reductions in cerebral blood flow and changes in depth of anaesthesia.[1 3] Therefore, it was assumed that there was a threshold brain concentration of propofol for the onset and offset of loss of consciousness. While the magnitude of this threshold depends on the magnitude of the pharmacodynamic response to propofol in the brain, the level of surgical stimulus and other factors, this analysis is valid for comparison purposes. A value of 2 mg litre^{-1} was chosen for the threshold, which was consistent with our previous observations.[3] Note that as the brain was modelled as an apparent distribution volume, 2 mg litre^{-1} is an apparent brain concentration which must be multiplied by the brain:blood partition coefficient to give the true brain concentration.[6] The time of onset of anaesthesia (loss of consciousness) was the time the apparent brain concentrations first reached 2 mg litre^{-1}, the time of maximum depth of anaesthesia was the time of peak brain concentrations (expressed as percentage of normal for comparison purposes), while duration of anaesthesia was the length of time the brain concentrations remained greater than 2 mg litre^{-1}.

R. N. UPTON, BSC, PHD, G. L. LUDBROOK, MB, BS, FANZCA, Department of Anaesthesia and Intensive Care, Royal Adelaide Hospital, University of Adelaide, North Terrace, Adelaide, SA 5005, Australia. Accepted for publication: May 26, 1997.
Correspondence to R. N. U.

The predictions of the model were examined for two dose regimens of propofol—a bolus injection of 200 mg over 20 s ("bolus") and an infusion of 40 mg min^{-1} for 5 min ("infusion"). These correspond in general terms to the two major clinical methods used for induction of anaesthesia with this agent.

STRUCTURAL ANALYSIS

The importance of various structural components of the model was analysed by systematically removing them from the model; these were drug-induced changes in cerebral blood flow, recirculation, hepatic clearance and vascular mixing.

SENSITIVITY ANALYSIS

The sensitivity of the model to changes in various variables was examined by introducing variability into one variable at a time: the variables examined were cardiac output, cerebral blood flow, systemic distribution volumes, lung extraction and lung distribution volume. Simulations were performed with these variables set at their normal value, and at values 50% higher and 50% lower than normal (see tables 2 and 3 for actual values used). For lung extraction, simulations were performed with lung extraction at constant values of 15%, 30% and 60% rather than the usual non-linear extraction.

IMPLICATIONS FOR DOSE REGIMENS

The model was used to examine the dose requirements of propofol to achieve a given level of anaesthesia for two administration paradigms. First, the optimum duration of injection of propofol was determined by simulations for a range of durations of injections while varying the dose until a peak brain concentration of 2 mg $litre^{-1}$ was achieved in each case. The required dose, time to peak arterial and brain propofol concentrations, and magnitude of peak arterial propofol concentrations were related to duration of injection. Second, to mimic the clinical practice of infusion with titration to a given anaesthetic end-point, the model was used to simulate infusions of propofol at rates of 50, 100 and 200 mg min^{-1} with administration stopped when a brain concentration of 2 mg $litre^{-1}$ (nominally loss of consciousness) was achieved. For each administration rate, the total dose administered at the time of the end-point, time that end-point was reached and resulting time course of brain concentrations predicted by the model were recorded. These data were also compared with data in humans of Peacock and colleagues[7 8] and Stokes and Hutton.[9]

Results

A TYPICAL OUTPUT OF THE MODEL

Arterial and brain concentrations of propofol expected after bolus and infusion regimens for the normal cardiac output state are shown in figure 1. It is apparent that arterial concentrations of propofol are relatively transient, particularly after bolus administration. For the same dose, the infusion regimen delayed the onset of anaesthesia rather than affecting its depth, compared with the bolus. Thus

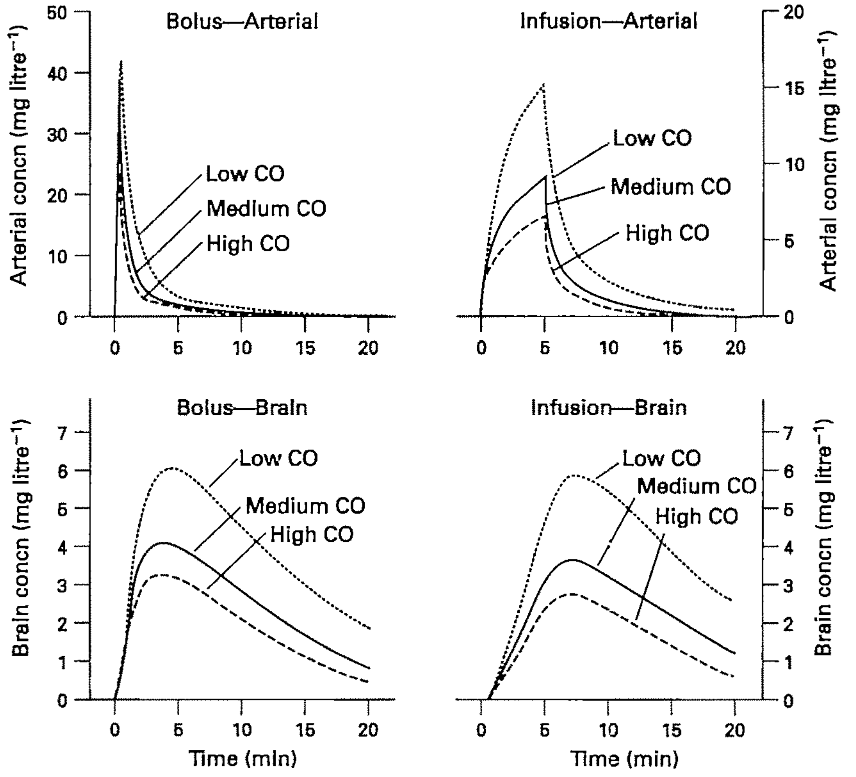

Figure 1 Typical outputs of the model, also showing the sensitivity of the model to changes in cardiac output (CO). Data were simulated with CO at its normal baseline value (medium), and at a value 50% lower (low) or 50% higher (high) than normal.

Table 1 Structural analysis. Analysis of the effect of removing various components of the model on the peak concentration in arterial blood and brain, time of onset of anaesthesia, peak level of anaesthesia as a percent of normal and time of this peak, and total duration of anaesthesia. CBF=Cerebral blood flow

Analysis	Peak arterial (mg litre^{-1})	Peak brain (mg litre^{-1})	Onset time (min)	Peak effect (% normal)	Peak time (min)	Duration (min)
Bolus						
Normal	38.03	4.07	1.15	100	3.9	12.6
No CBF changes	38.14	4.49	1.05	110	3.4	9.7
No recirculation	37.83	2.47	1.45	61	2.8	4.05
No hepatic clearance	38.14	4.15	1.15	102	4.1	15.05
No vascular mixing	39 56	3.80	1.15	93	3 8	11.65
Infusion						
Normal	9.00	3.66	3.5	100	7.1	12 4
No CBF changes	9.00	4.53	3.25	124	6.6	10.6
No recirculation	5.95	2.77	3.85	75	5.9	5.95
No hepatic clearance	9.39	3.80	3.45	104	7.5	15.45
No vascular mixing	9.08	3.68	3.45	101	7.1	12.5

infusion of the same dose as used for the bolus caused a 10% decrease in the maximum depth of anaesthesia, but only a 1.5% reduction in duration of anaesthesia. However, the time of onset of anaesthesia was increased from 1.15 to 3.5 min, while the time of maximum depth of anaesthesia was increased from 3.9 to 7.1 min.

STRUCTURAL ANALYSIS

The structural analysis is summarized in table 1. Removing propofol-induced reductions in cerebral blood flow from the model caused insignificant changes in peak arterial concentrations for either dose regimen. This suggests that the contribution of recirculated propofol from the brain to arterial concentrations is low when cerebral blood flow is a small fraction of cardiac output (as in sheep). However, the peak brain concentration was 10–12% higher, onset of anaesthesia earlier and duration of anaesthesia 15–25% less in the absence of propofol-induced reductions in cerebral blood flow. This taller but narrower peak in brain concentrations is entirely consistent with, and characteristic of, the higher average flow in this situation.[10]

The effect of removing recirculation, effectively making the model show the first-pass passage of the injected peak of propofol, differed with the dose regimen. The peak arterial concentration was unaffected by the absence of recirculation for the bolus regimen, but was significantly lower for the infusion. Without recirculation peak brain concentrations of propofol were 61% and 75% of normal for the bolus and infusion, respectively, but duration of anaesthesia was substantially shorter than normal.

Removing hepatic clearance from the model caused only a minor increase in peak arterial propofol concentrations, and its effect was similar for both dose regimens. Peak brain concentrations were altered by less than 4%, but the absence of hepatic clearance decreased the rate of elution of propofol from the brain and prolonged the duration of anaesthesia.

Removing the vascular mixing component of the model resulted in only minor changes in the time course of anaesthesia, but was more important for the bolus regimen.

SENSITIVITY ANALYSIS

Altering cardiac output had a profound effect on both arterial and brain concentrations of propofol

Table 2 Sensitivity analysis for bolus dose. Peak arterial and brain concentrations, time of onset of anaesthesia, peak level of anaesthesia as a percent of normal and time of this peak and total duration of anaesthesia after bolus administration for various values of the variables of the model. CBF=Cerebral blood flow

Variable	Value	Peak arterial (mg litre^{-1})	Peak brain (mg litre^{-1})	Onset time (min)	Peak effect (% normal)	Peak time (min)	Duration (min)
Cardiac output	Low (2.8 litre min^{-1})	41.90	6.00	1.05	147	4.5	18.2
	Med (5.6 litre min^{-1})	**38.14**	**4.07**	**1.15**	**100**	**3.9**	**12.6**
	High (8.4 litre min^{-1})	32.77	3.24	0.75	80	3.8	9 9
CBF	Low (0.02 litre min^{-1})	38.90	2.61	2.1	64	5.1	10 7
	Med (0.04 litre min^{-1})	**38.14**	**4.07**	**1.15**	**100**	**3.9**	**12.6**
	High (0.06 litre min^{-1})	38.09	5.14	0.85	126	3.3	11 7
Tissue volumes	Low (50%)	38.37	4.83	1.15	119	4.4	13.9
	Med (100%)	**38.14**	**4.07**	**1.15**	**100**	**3.9**	**12.6**
	High (150%)	37.99	3.70	1.20	91	3.6	11.1
Lung ER	Low (15%)	34.25	4.40	1.15	108	4.2	16.3
	Med (30%)	28.19	3.59	1.35	88	3.9	11.9
	High (60%)	16.08	2.02	2.9	50	3.4	1
Lung volume	Low (1.8 litre)	58.75	4.92	0.85	120	3 5	14 2
	Med (3.6 litre)	**38.14**	**4.07**	**1.15**	**100**	**3.9**	**12.6**
	High (5.4 litre)	27.88	3.51	1 45	86	4.3	11.3

Table 3 Sensitivity analysis for infusion dose. Peak arterial and brain concentrations, time of onset of anaesthesia, peak level of anaesthesia as a percent of normal and time of this peak, and total duration of anaesthesia after infusion administration for various values of the variables of the model. CBF=Cerebral blood flow

Variable	Value	Peak arterial (mg litre^{-1})	Peak brain (mg litre^{-1})	Onset time (min)	Peak effect (% normal)	Peak time (min)	Duration (min)
Cardiac output	Low (2.8 litre min^{-1})	15.20	5.85	2.75	160	7.6	19.8
	Med (5.6 litre min^{-1})	**9.00**	**3.66**	**3.5**	**100**	**7.1**	**12.4**
	High (8.4 litre min^{-1})	6.53	2.77	4.35	75	6.9	7.8
CBF	Low (0.02 litre min^{-1})	8.98	2.56	5.1	69	8.32	10.4
	Med (0.04 litre min^{-1})	**9.00**	**3.66**	**3.5**	**100**	**7.1**	**12.4**
	High (0.06 litre min^{-1})	8.98	4.42	2.85	121	6.7	12.1
Tissue volumes	Low (50%)	10.55	4.20	3.3	115	7.5	13.4
	Med (100%)	**9.00**	**3.66**	**3.5**	**100**	**7.1**	**12.4**
	High (150%)	8.19	3.40	3.6	93	6.8	11.4
Lung ER	Low (15%)	8.65	3.73	3.5	102	7.5	15.4
	Med (30%)	6.69	3.01	4.05	82	7.1	10.4
	High (60%)	3.37	1.70		Not anaesthetized		
Lung volume	Low (1.8 litre)	9.53	3.87	3.1	106	6.8	13
	Med (3.6 litre)	**9.00**	**3.66**	**3.5**	**100**	**7.1**	**12.4**
	High (5.4 litre)	8.47	3.45	3.85	94	7.4	12.0

throughout the induction period for both dose regimens (fig. 1, tables 2 and 3). A four-fold *increase* in cardiac output (2.8 to 8.4 litre min^{-1}) produced a *decrease* in peak arterial and brain concentrations (to 78% and 54% of the low value for the bolus, and to 42% and 47% for the infusion, respectively). However, the time of these peak values were within 15% of each other, with the exception of the time to peak arterial concentrations after the bolus dose (from 0.5 to 0.3 min).

Altering cerebral blood flow had a minimal effect on arterial concentrations and, in comparison with cardiac output, had an opposing effect on brain concentrations of propofol. A four-fold *increase* in cerebral blood flow produced an *increase* in brain concentrations after the bolus to 196% of the low value, and this increase was also substantial (172%) for the infusion. However, higher peak brain concentrations were not associated with longer durations of anaesthesia, as the decline in brain concentrations was also more rapid.

The presence or absence of recirculation was found to substantially alter the time course of both arterial and brain propofol concentrations (table 1), but the model was less sensitive to the actual magnitude of the distribution volumes of the tissue pools that affected the extent of recirculation (tables 2 and 3). Larger tissue pools decreased peak arterial concentrations significantly for the infusion regimen, but the bolus was less affected. However, duration of anaesthesia was decreased to a similar extent for both regimens (15–20%).

Of more importance to the propofol concentrations achieved after both dose regimens was the magnitude of lung extraction (tables 2 and 3). While this is markedly non-linear in sheep,[1] this simulation showed what could be expected if extraction was set over a range of constant values. The extent of lung extraction greatly altered the magnitude of arterial concentrations. Peak arterial values decreased from 34.3 to 16.1 mg litre^{-1} for the bolus, and from 8.65 to 3.37 mg litre^{-1} for the infusion as lung extraction increased. Secondary to these altered arterial concentrations, brain concentrations also decreased with increasing lung extraction. At the highest value of lung extraction, brain concentrations were sufficiently low that propofol produced no anaesthesia. However, at anaesthetic concentrations, lung extraction of propofol is relatively low[1] and it is unlikely that high values of lung extraction would be encountered when it is used as an induction agent.

As the role of the lung in the metabolism of propofol is important, it may be expected that distribution of propofol into the lungs may also have a substantial effect on concentrations of propofol. However, the effect was relatively small for the infusion regimen, while more pronounced for the bolus (tables 2 and 3). In particular, the distribution volume of the lung had a clear role in attenuating peak arterial concentrations for this regimen.

IMPLICATIONS FOR DOSE REGIMENS

Effect of rate of administration

The effects of changes in the rate of injection on dose requirements to reach a peak brain concentration of 2 mg litre^{-1} are shown in figure 2A. The dose was minimized when propofol was administered over approximately 2 min, with peak brain concentrations reached at approximately 4.5 min. More rapid injection had little effect on the time to achieve peak concentrations in the brain (fig. 2B) but was associated with a large increase in peak arterial concentrations (fig. 2C). In general, peak brain concentrations (and therefore maximum depth of anaesthesia) lagged behind the end of the injection by approximately 3 min for these rapid injections, but this was reduced to approximately 2 min for the slower injections.

The effects of changing the rate of injection of a given dose (100 mg) are shown in figure 3. Decreasing the duration of injection to less than 1 min produced little effect on peak brain concentrations, but was accompanied by large increases in arterial concentrations.

For infusion with titration to an end-point, the

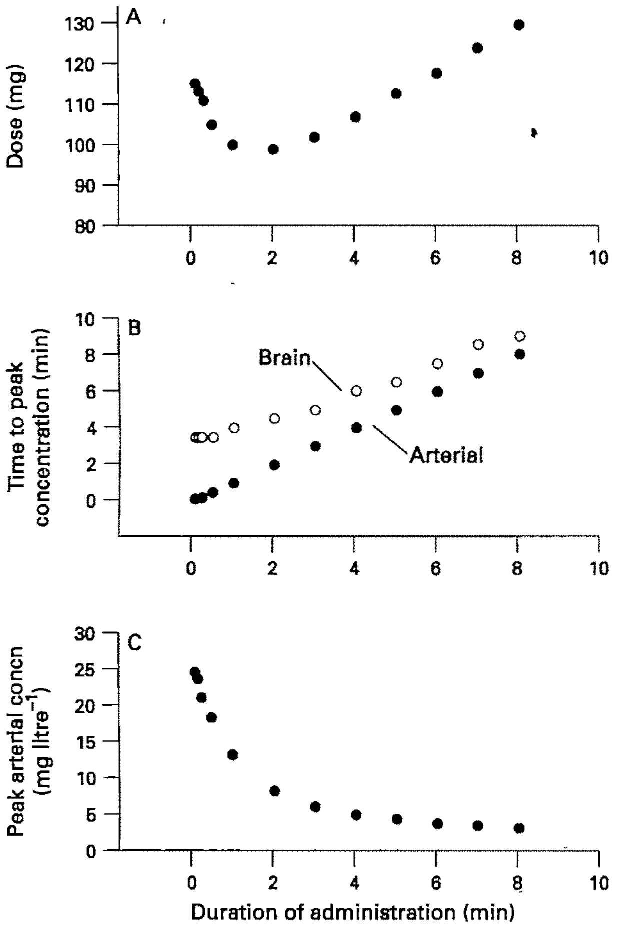

Figure 2 Effects of duration of administration on: (A) dose required to reach a peak brain concentration of propofol of 2 mg litre^{-1}; (B) concurrent times to reach peak concentrations in arterial blood (●) and brain (○); and (C) concurrent peak arterial concentrations achieved.

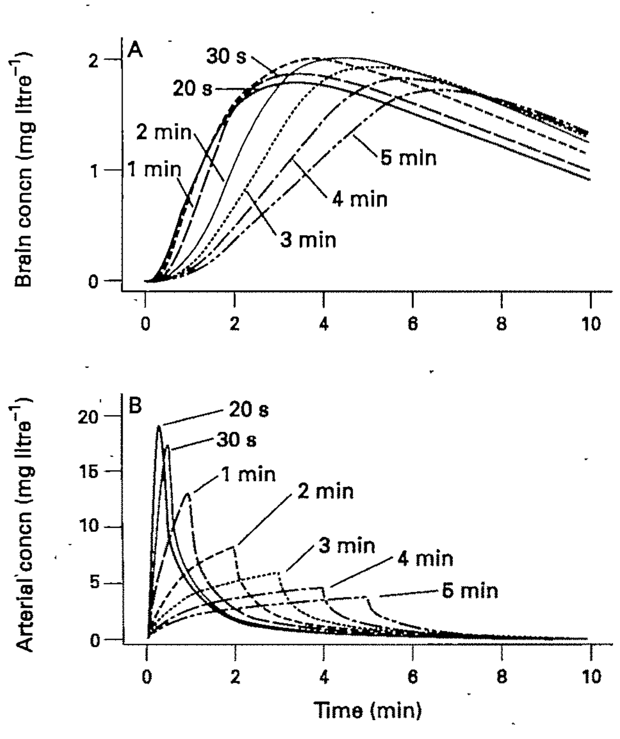

Figure 3 Simulation of administration of propofol 100 mg at different rates of injection on the time course of concentrations in the brain (A) and arterial blood (B).

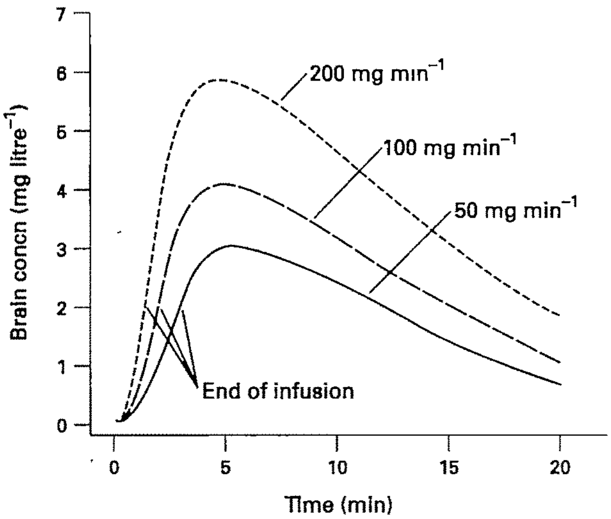

Figure 4 Titration by infusion. Simulation of the time course of brain concentrations of propofol when administered at different infusion rates, with infusions ceased when a brain concentration of 2 mg litre^{-1} was reached.

profile of brain concentrations at different infusion rates is shown in figure 4. Note that the peak brain concentrations occurred approximately 3 min after cessation of the infusion, and that the highest infusion rate was associated with peak brain concentrations 2–3 times higher than those chosen as the end-point. The corresponding total doses administered and the time of onset of anaesthesia are shown

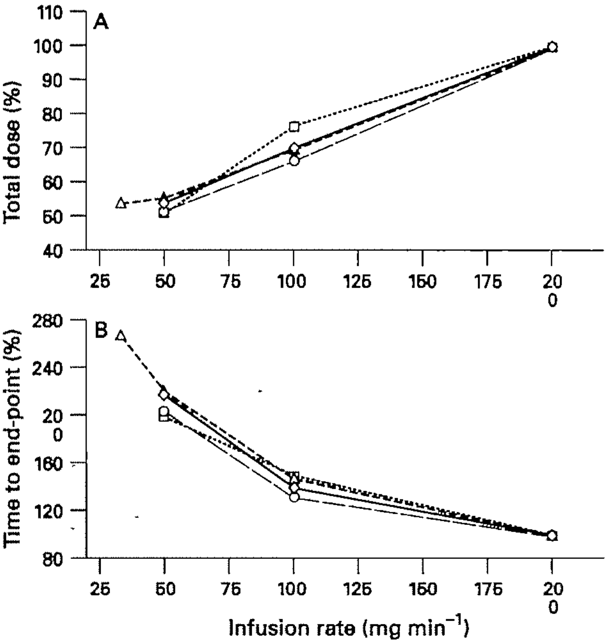

Figure 5 Comparison of the predictions of the model with data from humans on the influence of decreasing the infusion rate of propofol when titrating to a given anaesthetic end-point. Total administered dose (A) and time of onset of the anaesthetic end-point (B) are shown for the model based on data in sheep (solid line) and for the data in humans of Stokes and Hutton (□),[9] Peacock and colleagues 1990 (○)[7] and the young patient group of Peacock and colleagues 1992 (△).[8] As different anaesthetic end-points were used in each study, the total dose and time to end-point are expressed as a percentage of the fastest infusion rate. Data for the old patient group from the latter study could therefore not be presented in this format, as no 200 mg min^{-1} dose was given.

in figure 5. Lower infusion rates were associated with a slower onset of anaesthesia, lower total doses at the point of onset of anaesthesia and lower peak brain concentrations after cessation of administration.

Discussion

The principal purpose of this model was to consolidate experimental data from a chronically instrumented sheep preparation.[2 3] It is important to remember that the model has therefore been validated extensively against a comprehensive *in vivo* data set[1] comprising measurements of blood flows and propofol concentrations in several sites, rather than the more traditional single set of arterial or venous blood concentrations. This greatly increases the physiological "fidelity" of the model.

MODEL ANALYSIS

Most features of the model had a significant influence on the output of the model, and their inclusion would seem reasonable on more than theoretical grounds. Interestingly, the value of some features depended on the administration regimen. In particular, the bolus regimen was influenced by the vascular mixing and lung kinetic components, highlighting the crucial role of these systems as "capacitors" or stores of drug after rapid injection.[11 12]

Two of the features of the model were analysed for mechanistic reasons only. Recirculation of drug is clearly unavoidable, and is an integral part of the induction process (table 1). However, it is surprising to what extent first-pass passage of the injected peak contributes to induction of anaesthesia (approximately 60% of the peak anaesthesia and 33% of its duration). Recirculation of drug is often thought to occur rapidly (seconds rather than minutes), a situation that is not consistent with drugs such as propofol with high distribution volumes in tissues. The vascular mixing component of the model is compatible with our previous experimental observations of injection site to pulmonary artery transit[13] and contributes to the accurate description of kinetics after very rapid injections.

The remaining features of the model have more physiological significance, and will be discussed in turn.

DOSE AND INJECTION RATE

Rapid rates of injection of a dose of propofol achieved little in terms of increased depth of anaesthesia, but hastened its onset at the expense of markedly increased peak concentrations in the arterial system (fig. 2). While the significance of high initial concentrations in arterial blood vessels is not clear, arterial and venous dilatation are major contributors to hypotension during induction with propofol and may relate to direct exposure to vascular smooth muscle.[14–16] It is probably this effect that produces an increased incidence of hypotension with propofol compared with thiopentone, as both agents have a similar effect on myocardial contractility.[17]

For a given dose of propofol, very rapid injections appear to produce a peak in arterial concentrations that is too transient to fully load the brain with propofol (fig. 2), while for very slow injections peak brain concentration can be attenuated by metabolism and redistribution of the dose before the time of the peak (fig. 3). Consequently, there appears to be an optimal duration of injection of a given dose of propofol (2 min) for maximum depth of anaesthesia. Thus the model predicts that there are two possible benefits of administration of propofol over 2 min rather than the more traditional bolus—a direct dose-sparing effect and reduced peak arterial concentrations which may have a haemodynamic advantage.

When titrating to an anaesthetic end-point, it has been shown previously that slower rates of infusion of propofol reduce the total dose administered.[7–9] It has been speculated that this may be because of more propofol being "in transit" between the injection site and brain at higher infusion rates,[18] and this is confirmed in figure 4. For higher infusion rates, brain concentrations increased rapidly and continued to increase prodigiously after cessation of infusion, because of the greater mass of propofol stored in venous blood and lungs that had yet to reach the brain. Slower infusion rates were associated with slower increases in brain concentrations with better titration against the end-point, and minimized this "overshoot" in brain concentrations. The dose-sparing effect of the slower infusion is an illusion in the sense that although less propofol was used to reach the end-point, the total amount of anaesthesia produced (the AUC of the brain concentrations), particularly after cessation of infusion, was also significantly less. Regardless, there are considerable benefits in using the slower rate in that it reduces the profound increase in depth of anaesthesia after the desired end-point.

CARDIAC OUTPUT

Cardiac output was an important factor affecting induction of anaesthesia, with increased cardiac output decreasing depth and duration of anaesthesia. While the initial effect of cardiac output would be expected on the basis of indicator dilution principles before recirculation,[13] it is surprising that it persisted throughout the study. This is likely to be a result of the influence of cardiac output on tissue distribution in the model, which is reinforced by an increasing number of studies,[19–22] and is a feature of other physiological models.[23 24] Indeed, this growing evidence suggests that cardiac output may be a clinically significant determinant of the induction process, and a widely neglected pharmacokinetic variable.

Cardiac output can be subject to large changes *in vivo* because of factors such as age, anxiety or co-administration of other drugs, and the model predicted that these changes would also influence induction of anaesthesia with propofol. This is confirmed to some extent by the recent work suggesting that co-administration of esmolol, a beta blocker, provided a large dose-sparing effect on propofol requirements during induction of anaesthesia,[25] a phenomenon consistent with the cardiac output lowering effect of esmolol. The contribution of this process to the dose-sparing effect observed with other co-induction agents is as yet unknown.

CEREBRAL BLOOD FLOW

Cerebral blood flow was also a substantial determinant of the induction process, with increased cerebral blood flow increasing depth of anaesthesia, but causing relatively small changes in its duration. The fact that propofol reduces cerebral blood flow by up to 50%, thereby altering its own kinetics in the brain, was a significant feature of the induction process resulting in a lower mean cerebral blood flow and prolongation of the duration of anaesthesia by almost 3 min. There have been few experimental studies to confirm the role of cerebral blood flow in the induction process, although we have confirmed the cerebral kinetic implications of altered cerebral blood flow for propofol.[26] Cerebral blood flow would be expected to change *in vivo*, particularly in response to changes in carbon dioxide tension in the blood (e.g. after hyperventilation and by states such as anxiety), and the model predicts that these changes would also influence induction of anaesthesia with propofol.

TISSUE DISTRIBUTION VOLUMES

As for thiopentone,[27] distribution into systemic tissues contributed to the decline in arterial concentrations of propofol (tables 2 and 3), although clearance by the lung was also a significant factor for lower doses of propofol in this species. As expected, smaller tissue volumes increased the rate of recirculation of propofol, but the model was relatively insensitive to changes in the magnitude of the tissue distribution volumes. These volumes are a composite term incorporating the physical volumes of these tissues, their lipid content, extent of blood and tissue protein binding, and partitioning of ions across pH gradients.[28] The changes simulated were relatively large—it is not clear to what extent these changes can be accounted for *in vivo* by alterations in factors such as protein binding of propofol within and between individuals. For example, a four-fold increase in apparent tissue volume would require a decrease in the fraction bound in blood from 90% to 22.5%.

LUNG KINETICS

While the lung kinetics of propofol were shown to be important factors in the induction process, the significant kinetic process was not distribution, but metabolism, particularly for lower doses. Both processes have been demonstrated to occur in the lungs for a variety of drugs.[29] Unfortunately, current double indicator methods for studying lung kinetics after bolus administration[12 30] are poor at differentiating between metabolism and distribution. Extensive, saturable conjugation of phenol by the lungs after bolus administration has been identified in rats, however,[31 32] and provides support for such a mechanism underlying the observed extraction of the phenol, propofol, after rapid administration to sheep.

CLEARANCE

In this study, clearance via the lungs was the only significant route of elimination for propofol during induction. Although hepatic clearance of propofol is sheep is large (approximately 87% extraction[4]), it had a relatively small effect on the induction process. By removing hepatic clearance, onset time and peak depths of anaesthesia were changed little, although duration of anaesthesia was increased by 2.5–3 min. This is consistent with reports of declines in propofol blood concentrations in anhepatic individuals.[33] Thus even large variations in hepatic enzyme efficiency caused by processes such as enzyme induction or inhibition would be expected to have minimal effects on the induction process.

IMPLICATIONS FOR HUMANS

Clearly, the basic mechanisms of kinetics and dynamics discussed in this article can be studied only in animals. The mechanisms described are valid for sheep, for which the variables of the model were estimated from an extensive *in vivo* data set. The technique of examining arterio-jugular gradients of drugs may be used to re-parameterize the model for humans,[34] particularly if cerebral blood flow is measured concurrently.[35] There is some evidence that the changes needed are not great with respect to initial bolus kinetics. The general size of the heart–lung system and cardiac output of a 50-kg sheep are similar to those of a 70-kg human, although the fraction of cardiac output reaching the brain is much reduced.[36] However, as relative perfusion of the brain is comparable with humans and cerebral blood flow responses to drugs in sheep have been found to be similar to those in humans,[2 37] the time course of the brain concentrations is also similar. The evidence for substantial lung extraction of propofol in humans is ambiguous, although it should be noted that clearance of propofol in humans often exceeds the expected liver blood flow. The data of Major and colleagues[38] showed large gradients across the lung, while Gray and colleagues[33] reported no gradient in anhepatic individuals. It is evident, however, that this extraction is relatively low at blood concentrations of propofol used clinically to induce anaesthesia, and so inter-species differences are likely to be relatively insignificant.

Despite these considerations of species differences, it is worth noting the very close agreement between the effects of the rate of propofol administration on induction dose and time to onset of anaesthesia between the current model and data in humans by different investigators (fig. 5). This suggests that the fundamental principles of distribution after bolus administration of propofol are similar between sheep and humans, and that the model, as presented, provides a valuable tool for designing further studies of induction of anaesthesia with propofol in sheep and humans. We advance the following hypotheses arising out of this work.

(1) There is little benefit in injecting propofol more rapidly than over 2 min. More rapid administration does not greatly increase the rate of induction, and potentially may increase the risk of hypotension because of high arterial concentrations.

(2) For titration of depth of anaesthesia with small bolus doses or infusion, a period of 2–3 min should be allowed between cessation of the dose and assessment of the level of anaesthesia in order to ensure the maximum depth of anaesthesia has been achieved.

(3) The effect of many clinical scenarios on propofol dose requirements (such as anxiety, hyperventilation, extremes of body weight and co-administration of other drugs) can be interpreted in terms of their primary effect on cardiac output and cerebral blood flow. Thus selection of a dose regimen for propofol may be best determined by consideration of these two factors.

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Overestimation of low cardiac output measured by thermodilution

J. P TOURNADRE, D. CHASSARD AND R. MUCHADA

Summary

We have investigated the influence of a cold water bolus (CWB) injection on overestimation of cardiac output (CO) in low CO states in anaesthetized dogs. CO was measured using three methods: (1) thermodilution (TD), (2) electromagnetic (EM) flow meter placed on the pulmonary artery and (3) transoesophageal echo-Doppler (OD) placed on the descending aorta. Measurements of CO were obtained before (steady state) and after induction of a low CO state with thiopentone 5 mg kg^{-1} i.v. After CWB injection, mean CO measured by EM and OD increased by 26% and 27%, respectively ($P<0.05$) during steady state, and by 85% and 75% ($P<0.05$) during the low CO state. This transient increase was produced by an increase in stroke volume, while heart rate did not change. Frank Starling's law may explain this variation by a sudden increase in preload produced by CWB injection. These results indicate that thermodilution overestimated CO during low CO states when CWB injection was used. (*Br. J. Anaesth.* 1997; **79**: 514–516).

Key words
Heart, cardiac output. Measurement techniques, cardiac output. Measurement techniques, thermodilution. Measurement techniques, transoesophageal Doppler. Measurement techniques, flowmetry. Dog.

Several methods have been used to measure cardiac output (CO) in humans. The thermodilution method (TD), described initially by Fegler,[1] has been used for 20 yr since its development with the catheter described by Swan and Ganz.[2] Several studies have demonstrated good overall agreement between TD and other methods estimating CO. However, several studies have shown that the TD method overestimates CO in the low range.[3–5] This was explained by heat loss during measurement.[3]

In our clinical anaesthetic practice, we observed in patients in whom CO was recorded simultaneously by TD and transoesophageal echo-Doppler (OD), an increase in CO measured by OD, immediately after injection of an iced water bolus. Therefore, this study was designed to investigate the effect of an iced temperature injectate on CO measured by TD, OD and by an electromagnetic (EM) flow meter placed on the pulmonary artery of anaesthetized dogs during normal and low CO states.

Materials and methods

After approval from our institutional Animal and Care Committee, six dogs (weight 18 (SD 5) kg) were anaesthetized with thiopentone 5 mg kg^{-1}, vecuronium 0.08 mg kg^{-1} and phenoperidine 0.015 mg kg^{-1}. The trachea was intubated and the lungs ventilated mechanically (Bird Mark 8, Products Corporation, Palm Springs, CA, USA) at an FI_{O_2} of 1, ventilatory frequency 20 bpm and tidal volume 10 ml kg^{-1}. Anaesthesia was maintained with phenoperidine 0.02 mg kg^{-1} h^{-1} and vecuronium 0.04 mg kg h^{-1}.

A Swan–Ganz catheter was inserted into the pulmonary artery via the right external jugular vein under x-ray control (7F diameter, Edwards Laboratories, Irvine, CA, USA). Thermodilution CO was measured using triplicate injections of 5 ml of 5% dextrose at 2 °C (cold water bolus (CWB)) during end-expiration.

A 12-mm EM flow probe (In Vivo Metric, Healsburg, CA, USA) was placed around the pulmonary artery after dissection of the pulmonary trunk via a left-sided thoracotomy. Pulmonary blood flow (PBF) was measured continuously with an EM blood flow meter (FM 501, Carolina Medical Electronics, King, NC, USA).

A special echo-Doppler probe, described previously,[6] was used to measure aortic blood flow (ABF) using a transoesophageal echo-Doppler (OD) ultrasound method (Dynemo 3000, Sometec, Paris, France). ABF, PBF, ECG and heart rate (HR) were recorded simultaneously and continuously before, during and after CWB injection.

Measurements were made with both continuous methods (PBF, ABF) after 15 min of steady state following surgical preparations and were repeated after injection of thiopentone 5 mg kg^{-1} i.v. to obtain a low CO state.

Instantaneous blood flow variations were measured by EM flow meter and OD methods during CWB injection. These measures were integrated by planimetry to calculate the average stroke volume (SV) on seven cardiac cycles. These

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J. P TOURNADRE*, MD, D. CHASSARD, MD, PHD, Critical Care Division, Hôpital de l'Hôtel-Dieu, 69002 Lyon, France. R. MUCHADA, MD, Critical Care Division, Clinique Mutualiste E. André, 69003 Lyon, France. Accepted for publication: June 3, 1997.

*Address for correspondence: Département d'Anesthésie-Réanimation, Hôpital de l'Hôtel-Dieu, 69002 Lyon, France.

were identical to cycles sampled during inscription of the TD curve.

Data are expressed as mean (SD) and were compared by Wilcoxon's test between the two states and by one-way analysis of variance (ANOVA) for haemodynamic data obtained by the different methods. Results were considered statistically significant at $P<0.05$.

Results

Results are summarized in table 1.

In all cases injection of thiopentone 5 mg kg^{-1} produced a decrease in HR and SV. For all measurement techniques there was a decline in CO after thiopentone ($P<0.05$). HR remained unchanged throughout the course of injection of the CWB using the TD method. CO values obtained by TD were higher than those obtained by the two other methods ($P<0.05$). The differences recorded with the other methods were more important during low CO states.

Table 1 Mean (SD) pulmonary blood flow (PBF), aortic blood flow (ABF) and cardiac output (CO) (measured by the thermodilution method) at steady state and after injection of thiopentone 5 mg kg^{-1} (low CO state). *$P<0.05$ *vs* before injection of the cold water bolus (CWB);.†$P<0.05$ *vs* steady state

	Steady state	Low CO state
HR (beat min^{-1})	137 (22)	120 (19)†
PBF (ml min^{-1})		
Before CWB	1583 (253)	1086 (297)†
After CWB	1988 (430)*	2035 (378)*
ABF (ml min^{-1})		
Before CWB	1382 (294)	947 (287)†
After CWB	1722 (391)*	1682 (281)*
OD (ml min^{-1})	2067 (466)	1847 (315)†

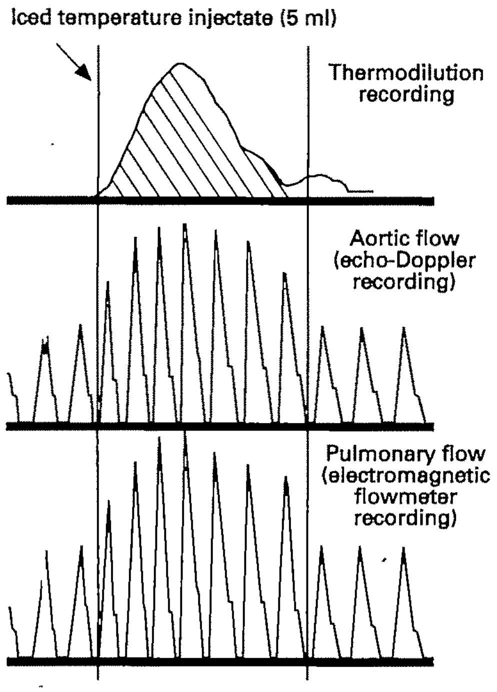

Figure 1 Effect of a cold water bolus (iced temperature) injection on stroke volume measured in the descending aorta and pulmonary artery in a dog with a low cardiac ouput.

CWB injection induced significant increases in PBF and ABF ($P<0.05$) (fig. 1). These increases were found in the two states but were proportionally more important during the low CO state.

Differences between the results of TD and those of pulmonary flow meter and aortic OD obtained after injection of CWB were not statistically significant. After CWB injection, CO, measured using EM and OD, increased by 26% and 27%, respectively, during steady state ($P<0.05$), and by 85% and 75% during low CO state ($P<0.05$).

Discussion

Data from previous studies showed that the TD method overestimated measurement of CO in patients with low CO states. This could explain the weak correlation between measurements by TD and other methods, such as the Fick method, during low CO conditions,[7 8] dye dilution techniques[9] and EM flow meter on the pulmonary artery.[10] These studies attributed differences to heat loss under conditions of low flow.[3–5 11–13] Our study did not evaluate this phenomenon during high output states as previous studies found a good correlation between TD and other methods under these conditions.[2 3]

In the course of the two CO states evaluated in our study (steady and low CO state), TD overestimated CO values compared with EM flow meter and OD (note that these two methods are performed in two different anatomical sites, the pulmonary artery and descending aorta, respectively). This was more significant in the presence of a low CO state. ABF was lower by 13–17% compared with PBF under all conditions. This can be explained by the fact that measurements at this level of the aorta do not take into account blood flow to the upper extremities, head, bronchial tubes and cardiac areas.

The increase in aortic flow was lower than that of pulmonary flow (75% and 85%, respectively, $P<0.05$) during the low CO state. This may reflect a septal shift in response to substantial increases in right ventricular end-diastolic volume that might transiently decrease left ventricular end-diastolic volume because of the restrictive effects of the pericardium. Thus aortic flow would be lower than pulmonary flow.

We found that CO, when measured by EM or OD, increased in all cases after administration of CWB injection. This transient increase was produced by an increase in SV over several cardiac cycles, while HR remained unchanged. During rapid injection of CWB into the right atrium, a transient increase in CO could increase SV by increasing preload. Frank Starling's law may explain this variation by a sudden increase in preload after CWB injection. This also explains why the phenomenon is more significant at low compared with normal CO states.

The increase in SV after injection of the CWB occurred without a change in HR. This may have resulted from the use of thiopentone. Its effect on the autonomic nervous system[14] prevents the sinus bradycardia caused by CWB injection described by Harris and colleagues[15] and Nishikawa and Dohi[16 17] under similar conditions. Because CO=SV×HR, a decrease in HR may balance the increase in SV. This may explain the good correlation between CO determination with TD and other methods, even in low CO states.[7,18–20] However, when HR is unchanged, especially in low CO states, the transient increase in SV could be responsible for discrepancies between TD and other methods of measurement of CO.[3,8,11,21]

With the TD method,[19] CO output is measured in the course of the first cardiac cycles after injection of the CWB. We found that SV increased after injection of the CWB compared with basal values. Thus the calculated output is overestimated. It is remarkable to note that when we measured outputs by EM and OD after CWB injection, we found values close to those obtained by TD during steady state or low CO. One can therefore estimate that, in our study, CWB injection induced the major part of the overestimation. The potential human implications of these findings need to be verified.

We used iced temperature injectates rather than room temperature injectates, as first described by Swan and Ganz.[2] To eliminate the influence of temperature induced by cardiac reflexes,[16,17] a study should be performed under the same conditions.

Accurate measurement of CO is an important goal in the management of anaesthetized or critically ill patients with compromised cardiac function. Our findings showed that thermodilution overestimated CO during low CO states when iced temperature injectates were used. This suggests that other non-invasive methods are necessary to determine CO in patients with low output states.

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Effect of temperature on the solubility of desflurane, sevoflurane, enflurane and halothane in blood

G. G. LOCKWOOD, S. M. SAPSED-BYRNE AND M. A. SMITH

Summary

We have investigated the effect of temperature on the blood-gas solubility of desflurane, sevoflurane, enflurane and halothane. Blood was equilibrated with gas mixtures of known composition in open cuvette or closed flask tonometers over a temperature range of 29–39 °C, and the concentration of each anaesthetic in blood was measured at 37 °C by repeated headspace analysis using a gas chromatograph. Solubility increased by 5.4% of the solubility at 37 °C for each degree that equilibration temperature was reduced. This result was true for all anaesthetics in all blood samples, and is in keeping with results for other volatile anaesthetics. (*Br. J. Anaesth.* 1997; **79**: 517–520).

Key words

Anaesthetics volatile, desflurane. Anaesthetics volatile, enflurane. Anaesthetics volatile, halothane. Anaesthetics volatile, sevoflurane. Temperature, solubility. Solubility, temperature.

Measurement of anaesthetic partial pressure in blood is affected by temperature because of a concomitant change in solubility. The most direct solution to this problem is to measure every sample at the temperature at which it was sampled, but it is inconvenient to measure several samples at different temperatures and a correction factor is commonly used instead. Measurements of solubility at different temperatures, from which such correction factors may be derived, have been published for halothane, enflurane, isoflurane and older agents,[1–4] but we are not aware of similar publications for newer anaesthetics. We have therefore measured the effect of temperature on blood solubility for desflurane and sevoflurane, but have included halothane to confirm that the results of our method agree with standard values, and enflurane to confirm the observation that it is different from other volatile anaesthetics.[4]

Methods

After Ethics Committee approval, we obtained 25 ml of blood from healthy volunteers and patients undergoing major surgery. Two methods were used to prepare samples. In the first studies, 5-ml aliquots were placed in the cuvette of an Instrumentation Laboratory IL 237 tonometer and equilibrated in a gas flow of 200 ml min^{-1} of air containing a single agent (approximately 3% desflurane or 1% sevoflurane) at different temperatures over a range of 29–39 °C. Blood temperature within the cuvette was measured by a bead thermistor (Kanthal Tempmaster). At the end of the equilibration period (15 min at stable temperature) samples were obtained from the tonometer gas outflow and analysed in a gas chromatograph (GC, see below). The tonometer was opened and two 2-ml samples of blood were obtained consecutively into a 2.5-ml gas-tight syringe (SGE, Milton Keynes, UK) and transferred into 5-ml glass vials (actual volumes 4.77 (SD 0.03) ml) which were closed with screw caps fitted with Teflon-faced septa. In the later experiments we tonometered the entire blood sample in a closed glass flask. The flask was flushed with a gas mixture containing approximately 1% each of sevoflurane, enflurane and halothane (desflurane could not be separated easily and was not included) and then sealed using a cap with a Teflon-faced silicone septum. It was fitted into a weighted jacket to lie submerged on rotating rollers in a water bath. Every 15 min during equilibration the septum was pierced to allow manometric pressure measurement. If positive pressure was found it was vented and the process repeated, but if not samples were obtained. Two separate samples of the flask headspace were first obtained by puncturing the septum, aspirating a gas sample and injecting it into the GC. Blood was obtained by inverting the flask and again sampling through the septum, and 2 ml were transferred into each of two 5-ml vials. The flask septum was replaced with a new one, the water bath thermostat adjusted and the process repeated so that each sample was equilibrated at four or five temperatures from 28 to 39 °C.

Blood samples were analysed by a method which determines the total content of each anaesthetic in blood when it was originally placed in the vial. Blood-gas solubility was derived from this because

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G. G LOCKWOOD, MB, BS, FRCA, BSC, S. M SAPSED-BYRNE, AIBIOL, BSC, M A. SMITH*, BSC, MB, BS, FRCA, Department of Anaesthesia, Hammersmith Hospital and Royal Postgraduate Medical School, London W12 0HS. Accepted for publication: May 20, 1997.

*Present address: Department of Anaesthesia, Royal National Orthopaedic Hospital, Stanmore, Middlesex.

Correspondence to G. G. L.

the initial anaesthetic partial pressure in the tonometer was known. Blood-gas solubility at 37 °C was also derived in this analysis.[5] The vials containing samples of blood from the tonometer were agitated in a water bath at 37 °C for 15 min to equilibrate the anaesthetic between the blood and gas phases. The headspace gas of each vial was sampled through the septum and injected into the GC. The vial was then opened, 1 ml of blood aspirated into the 2.5-ml syringe (taking care to prevent bubbling) and transferred to a clean vial and capped. This second, new vial was agitated at 37 °C for 15 min and the headspace analysed in the same way.

All gas analysis was performed in duplicate. Gas was aspirated into a 100-μl gas-tight syringe (SGE) and flushed through the 20-μl loop of a six-way valve (Valco) on the inlet of the GC (Pye Series 204). The carrier gas was nitrogen flowing at 30 ml min^{-1}. A 0.9-m glass column (2 mm id) packed with 3% OV-17 on GasChrom Q and maintained at 125 °C was used when a single agent was being measured (giving a retention time of approximately 30 s). A 1.5-m column, packed similarly, was maintained at 60 °C with a carrier flow of 15 ml min^{-1} to aid separation of multiple agents (retention time up to 2 min). Anaesthetic was detected by a flame ionization detector operating at 175 °C. Output from the GC was collected by a Perkin-Elmer LCI-100 integrator.

The blood-gas solubility coefficient at 37 °C (λ_{37}) was derived by considering the amount of anaesthetic in the second vial before and after equilibration.

$$\text{Content before equilibration} = 1\ \text{ml} \times P_1 \times \lambda_{37} \tag{1}$$

where P_1 = partial pressure (expressed as a fraction of ambient pressure) of anaesthetic in the first vial after equilibration and 1 ml = volume of blood.

$$\begin{gathered}\text{Content after equilibration} = \\ 1\ \text{ml} \times P_2 \times \lambda_{37} + 3.77\ \text{ml} \times P_2\end{gathered} \tag{2}$$

where P_2 = partial pressure of anaesthetic in the second vial after equilibration and 3.77 ml = volume of air in the headspace.

No anaesthetic is lost from the vial during equilibration so these expressions are equal, and so

$$\lambda_{37} = \frac{3.77 P_2}{P_1 - P_1} \tag{3}$$

The amount of anaesthetic in the vial at the end of the first equilibration can now be calculated.

$$\begin{gathered}\text{Content of first vial after equilibration} = \\ 2\ \text{ml} \times P_1 \times \lambda_{37} + 2.77\ \text{ml} \times P_1\end{gathered} \tag{4}$$

This amount of anaesthetic was contained in 2 ml of blood in equilibrium with the gas mixture in the tonometer.

$$\begin{gathered}\text{Content of first vial before equilibration} \\ = 2\ \text{ml} \times P_0 \times \lambda_{\text{tono}}\end{gathered} \tag{5}$$

where P_0 = partial pressure of anaesthetic in the tonometer gas flow and λ_{tono} = blood-gas solubility coefficient at the temperature of equilibration.

Equating (4) and (5), and re-arranging we obtain:

$$\lambda_{\text{tono}} = \frac{2P_1 \times \lambda_{37} + 2.77 P_1}{2P_0} \tag{6}$$

If blood is equilibrated in the tonometer at 37 °C then $\lambda_{\text{tono}} = \lambda_{37}$ and it is possible to rearrange equation (6) to calculate P_0:

$$\text{Calculated } P_0 = P_1 \left(1 + \frac{2.77}{2\lambda_{37}}\right) \tag{7}$$

The difference between the calculated P_0 and the directly measured P_0 is an indication of the overall accuracy of our assay.

There is a final point to consider. P_1 and P_2 refer to the partial pressures of anaesthetic within the vial. During equilibration the total pressure within the vial increases as the headspace gas is warmed from room temperature to 37 °C and saturated with water vapour. (The tonometer gas is air carrying anaesthetic, so we can neglect any exchange of respiratory gases between blood and headspace gas.) The sample aspirated into the syringe is at ambient pressure, and the anaesthetic it contains is "diluted" by expansion to this pressure. The peak recorded from the GC must therefore be increased:

$$P_{\text{vial}} = P_{\text{GC}} \frac{310}{T_{\text{lab}}} \times 1.03 \tag{8}$$

where P_{vial} = partial pressure of anaesthetic in the vial, P_{GC} = partial pressure derived from the height of the GC peak, T_{lab} = laboratory temperature (K) and 1.03 = a factor to allow for humidity (although the headspace gas contains 6% water vapour, the gas in the syringe before injection into the GC is at room temperature, so it cannot contain more than 3% water vapour). P_{vial} is therefore approximately 8% greater than P_{GC}. Gas sampled from the flask tonometer was assumed to be saturated, but at ambient pressure, and therefore peak heights were multiplied by 1.03. Gas from the open cuvette tonometer was assumed to be dry and at ambient pressure, so no correction was made to the GC readings.

The temperature coefficient was given by the slope of the regression line of solubility coefficient on temperature, determined for each blood sample using a Microsoft Excel v4 spreadsheet. The equivalence of the two tonometers was tested by comparing the errors in measurement of sevoflurane partial pressure of blood equilibrated at 37 °C, using the Student's *t* test. Temperature coefficients of different anaesthetics were compared by non-parametric analysis of variance (Kruskal–Wallis). All statistical tests were calculated using Arcus Biomedical v6.8 on an IBM-compatible personal computer.

Results

In every sample we found a linear relationship between temperature and blood-gas solubility so that a temperature coefficient (defined as the slope of the temperature–solubility graph) could be determined

Table 1 Total number of samples, mean error of measured anaesthetic blood partial pressures of the samples equilibrated at 37°C, expressed as a percentage of the measured tonometer partial pressure and mean temperature coefficients

	Desflurane	Sevoflurane	Enflurane	Halothane
Total No. of samples (and No. at 37 °C)	59 (14)	127 (26)	101 (20)	101 (20)
Mean (SEM) error at 37 °C (% of tonometer partial pressure)	−5.8 (1.1)	−2.2 (1.4)	−5.5 (1.3)	−3.4 (1.4)
Mean (SD) temperature coefficient (°C^{-1})	−0.023 (0.003)	−0.030 (0.001)	−0.094 (0.008)	−0.100 (0.008)
Mean (SEM) $\lambda_{B/G}$ at 37 °C	0.52 (0.02)	0.62 (0.02)	1.50 (0.07)	2.00 (0.11)
Mean (SEM) temperature coefficient as a percentage of $\lambda_{B/G}$ at 37 °C (°C^{-1})	4.4 (0.2)	4.5 (0.2)	5.9 (0.5)	4.6 (0.4)

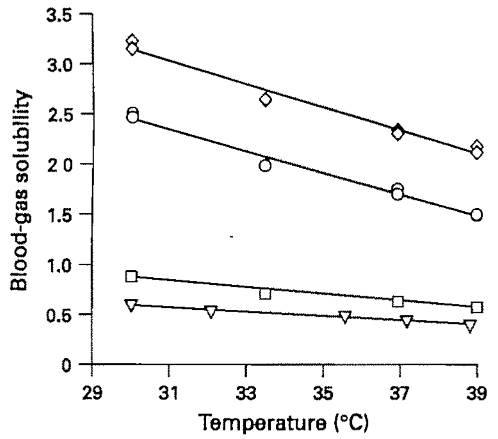

Figure 1 Typical results. Blood from one source was equilibrated with desflurane in an open cuvette. A different sample of blood was equilibrated with sevoflurane, enflurane and halothane simultaneously in a closed flask. Paired samples were obtained from the tonometers at different temperatures and regression lines are shown for desflurane (▽), sevoflurane (□), enflurane (○) and halothane (◇): the slope of the regression line is the temperature coefficient.

(fig. 1). Table 1 shows the mean error of measured anaesthetic blood partial pressures of the samples equilibrated at 37 °C, expressed as a percentage of the measured tonometer partial pressure, and summarizes our results. There were no differences in the sevoflurane results between blood equilibrated in the cuvette or flask. The temperature coefficient of enflurane, expressed as a fraction of blood-gas solubility at 37 °C, was significantly greater ($P<0.005$) than those of desflurane, sevoflurane and halothane, which were indistinguishable.

Discussion

We have used repeated headspace equilibration to determine the blood-gas coefficient. An alternative method is to vaporize a known amount of anaesthetic in a flask of known volume containing a known volume of blood. This has the advantage of being a single step technique, but the disadvantage that it is difficult to handle small quantities of liquid anaesthetic and there is no internal check for accuracy within the method. In contrast, when blood equilibrated in a tonometer at 37 °C is analysed by our method, we are able to calculate the initial partial pressure of anaesthetic at the time it was first sampled. If this calculation differs from the partial pressure of anaesthetic in the tonometer gas, it is known immediately that an error has occurred. The small deviations from the tonometer gas in our 37 °C samples justify our confidence in our methods.

We started with a commercial tonometer in which blood was equilibrated in an open cuvette. There are no concerns about pressure effects with this system, but we could not be sure of the humidity of the gas in the tonometer outflow, and the temperature of blood did not equilibrate with the water jacket and had to be measured directly. These disadvantages have been overcome in the simple, closed flask tonometer and we believe that with care we can ensure that the pressure within the flask is atmospheric, and therefore we now prefer this method.

Our two-stage headspace equilibration method determined the blood-gas coefficient at 37 °C and deduced the coefficient at other temperatures. Although it would have been simpler in principle to undertake the analysis of each 2-ml sample at its temperature of equilibration, this would have slowed the measurements greatly. At first sight, it would seem that this short-cut removes the internal check for accuracy within the method, but because one sample was equilibrated in the tonometer at 37 °C, it could be validated and its λ_{37} value assumed accurate. All samples have their blood-gas coefficient measured at 37 °C regardless of the temperature of equilibration in the tonometer and that can be compared with the validated result for the same blood sample. In practice no results were discarded on this basis.

Our results support an essentially linear relationship between temperature and solubility. In a comprehensive review of the subject, Allott and colleagues made the empirical observation that for any particular anaesthetic, the temperature coefficient was itself proportional to the logarithm of blood-gas solubility at 37 °C for that anaesthetic.[6] This relationship held over a very wide range of gases and vapours from nitrogen ($\lambda=0.014$) to diethyl ether ($\lambda=13$), but it was only one of three that could be justified on theoretical grounds. Our results suggested that, within the range of temperatures encountered clinically, a simpler relationship is adequate for modern, halogenated volatile anaesthetics: the temperature coefficient is proportional to blood-gas solubility at 37 °C. Our results went a little further. We obtained blood not only from starved, preoperative patients but also from post-prandial volunteers and patients during cardiopulmonary bypass so that for each anaesthetic we had a wide range of values of λ_{37}. For each agent studied, the effect of temperature on solubility was greatest on blood samples with the greatest solubility at 37 °C, as shown in figure 2. Logarithmic scales have been used to

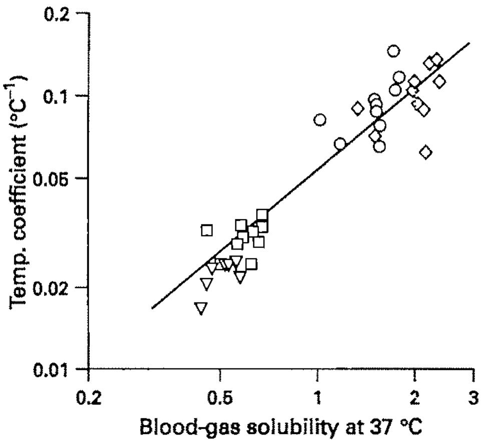

Figure 2 Dependence of the temperature coefficient on solubility at 37°C for desflurane (▽), sevoflurane (□), enflurane (○) and halothane (◇). Logarithmic axes have been used to expand the area of interest, but because the linear regression line passes through the origin, it remains straight on the logarithmic plot.

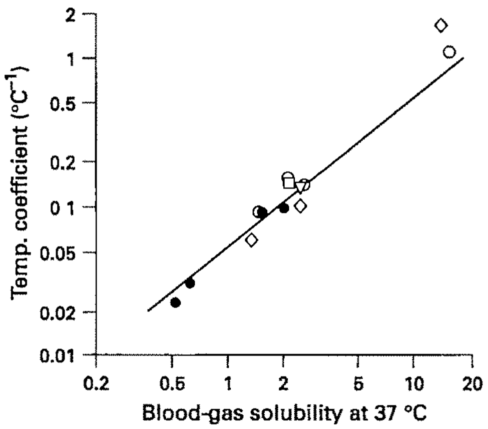

Figure 3 Dependence of the temperature coefficient on solubility at 37°C: mean results from our study and previous publications. Logarithmic axes have been used to expand the area of interest. The linear regression line derived from the data of the current study is shown: it passes through the origin so it remains straight on the logarithmic plot. ●=Present study (from left to right, desflurane, sevoflurane, enflurane and halothane); □=Han and Helrich[1] (halothane); ▽=Laasberg and Hedley-Whyte[2] (halothane); ◇=Stoelting and Longshore[3] (from left to right, fluroxene, halothane and methoxyflurane); and ○=Eger and Eger[4] (from left to right, isoflurane, enflurane, halothane, methoxyflurane).

expand the region of greatest interest, and are justified because the regression line drawn through our data passes through the origin (the sense of the temperature change has been reversed to allow a logarithmic transformation). Although the correlation is not significant for any individual anaesthetic, it is strongly significant when the results of all agents are pooled and the resulting temperature coefficient is −5.4% (95% CI −4.5%, −6.2%) of the solubility at 37 °C.

Figure 3 shows our mean results on the same plot as group results from other studies; the proposed linear correlation fits adequately and the significant difference found with enflurane is of little consequence. When the temperature coefficients for halothane from the studies cited previously are expressed in terms of solubility at 37 °C (6.5%,[1] 5.7%,[2] 4.6%,[3] 4.8%[4]), the most recent measurements are seen to agree closely with ours. Eger and Eger's result of 5.8% for enflurane also agrees well, giving us confidence in our method.

When measuring the partial pressure of an anaesthetic in blood, the temperature coefficient is used to correct for differences between blood temperature at the time of sampling and the temperature of the analysis. The 95% confidence interval for such a measurement is 5–10% of its value,[5] so a little uncertainty in the value of the temperature coefficient is tolerable. We therefore advocate the simple rule that the Ostwald solubility coefficient of anaesthetics in blood increases (or decreases) by 5.4% of the coefficient at 37 °C for every degree decrease (or increase) in temperature within the clinical range.

Acknowledgement

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British Journal of Anaesthesia 1997; **79**: 521–524

Studies on the binding of [^{3}H]amethocaine to rat cerebrocortical membranes

T. KUDO, M. KUDO, K. HIROTA AND D. G. LAMBERT

Summary

We have examined the binding of the local anaesthetic agent [^{3}H]amethocaine to rat cerebrocortical membranes. All studies were performed in Tris buffer 50 mmol litre^{-1} at pH 7.4. Bound and free radioligand were separated by rapid vacuum filtration. [^{3}H]Amethocaine binding at room temperature was dose-dependent and saturable, with mean K_d and B_{max} values of 153 (SEM 18) nmol litre^{-1} and 9.4 (1.6) pmol/mg protein, respectively. [^{3}H]Amethocaine binding was displaced in a dose-dependent manner (pIC$_{50}$) by unlabelled amethocaine (6.89), procaine (5.20), lignocaine (3.46) and prilocaine (2.81). Ropivacaine and bupivacaine did not produce 50% displacement at the highest concentrations used (10^{-4} and 10^{-3} mol litre^{-1}, respectively). We examined the nature of the binding site further with a range of ion channel antagonists (nifedipine, verapamil, diltiazem, ω-conotoxin, tetrodotoxin, tetraethylammonium and 4-aminopyridine) and ion channel coupled receptor ligands (L-glutamate, MK801, GABA, glycine and nicotine). With the exception of tetraethylammonium (pIC$_{50}$ 3.07) and 4-aminopyridine (pIC$_{50}$ 3.68), all non-anaesthetic agents failed to displace [^{3}H]amethocaine. Collectively our data suggest that it is unlikely that there is a single target site for all local anaesthetic agents. (*Br. J. Anaesth.* 1997; **79**: 521–524).

Key words
Anaesthetics local, amethocaine. Model, rat. Ions, ion channels.

It is well known that local anaesthetics interact with membrane Na$^+$ channels to inhibit information flow in neurones.[1–3] However, there is now growing evidence for an additional site(s) of action, including voltage-sensitive Ca^{2+} channels (VSCC).[4–7] Indeed, we have reported previously that a range of local anaesthetic agents at clinically relevant concentrations interact with L-type VSCC channels in rat cerebrocortical membranes.[8 9] We demonstrated that procaine, prilocaine, lignocaine, amethocaine and bupivacaine displaced the binding of an L-channel radiolabel, [^{3}H]PN200-110, with a rank order potency that correlated with the lipid solubility of these agents.[9] In this study we report dose-dependent and saturable binding of [^{3}H]amethocaine to rat cerebrocortical membranes and examine the effects of a range of local anaesthetic agents and transmitters/channel blockers with this binding site.

Materials and methods

MEMBRANE PREPARATION

All studies were performed in rat cerebrocortical membranes resuspended in Tris HCl 50 mmol litre^{-1}, pH 7.4 (prepared as described previously) by homogenization and centrifugation.[9 10]

[^{3}H]AMETHOCAINE BINDING ASSAY

In order to determine the maximum binding capacity or total number of binding sites (B_{max}) and the equilibrium dissociation constant for [^{3}H]amethocaine (K_d), membranes (approximately 50 μg of membrane protein) were incubated in 150-μl volumes with increasing concentrations (approximately 3–600 nmol litre^{-1}) of [^{3}H]amethocaine (>95% pure, 43 Ci mmol^{-1}, Amersham International, UK). In addition, we attempted to determine the K_d kinetically by measuring the ratio of the dissociation rate constant (K_{-1}) to the association rate constant (K_{+1}). In these studies, membranes (approximately 750 μg) were incubated in 1-ml volumes with approximately 1 nmol litre^{-1} of [^{3}H]amethocaine to equilibrium (>15 min at room temperature and >2.5 h on ice). At 60 min (room temperature) or 3 h (ice), dissociation was initiated by the addition of unlabelled amethocaine 1 mmol litre^{-1}.

For displacement studies the assay volume was 1 ml and a fixed concentration of [^{3}H]amethocaine (approximately 1 nmol litre^{-1}) was used. Agents that displace [^{3}H]amethocaine are likely to interact at the same target site or to be coupled allosterically to the [^{3}H]amethocaine binding site. Increasing concentrations of unlabelled amethocaine, lignocaine, procaine, prilocaine, bupivacaine and R(+)/S(−)ropivacaine were added and the

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T. KUDO, MD, M. KUDO, MD, K. HIROTA, MD, D. G. LAMBERT, PHD, University Department of Anaesthesia, Leicester Royal Infirmary, Leicester LE1 5WW. Accepted for publication: June 2, 1997.

Correspondence to D. G. L.

concentration producing 50% displacement (IC_{50}) determined. In addition, displacement studies were performed with the following ion channel blockers/transmitters in order to examine the site(s) of interaction: nifedipine, verapamil, diltiazem (L-type VSCC blockers), ω-conotoxin GVIA (N-type VSCC blocker), tetrodotoxin (Na^+ channel blocker), tetraethylammonium (K^+ channel blocker), 4-aminopyridine (4-AP; K^+ channel blocker), L-glutamate, MK801 (NMDA receptor ion channel blocker), GABA, glycine and nicotine. In all experiments non-specific binding (NSB) was defined in the presence of excess (1 mmol $litre^{-1}$) unlabelled amethocaine. Saturation, kinetic and amethocaine isotope dilution studies were performed at either room temperature (approximately 23 °C) or on ice (approximately 0 °C to limit ligand dissociation). Bound and free radioligand were separated by rapid vacuum filtration.

DATA ANALYSIS

All data are presented as mean (SEM) (*n*). Saturation data were analysed according to Scatchard.[11] Observed association (K_{ob}) and dissociation (K_{-1}) rate constants were estimated from non-linear, one-phase exponential association and dissociation equations using Graphpad-Prizm. K_{ob} was corrected for K_{-1} and the concentration of [^{3}H]amethocaine to yield K_{+1}. K_d was then calculated using K_{-1}/K_{+1}. The concentration of displacing drug producing 50% displacement of specific binding (pIC_{50}) was estimated from individual curves by non-linear regression (Graphpad-Prizm). In some experiments 100% displacement was not achieved and data were analysed based on an assumed 100% displacement.

Results

Binding of [^{3}H]amethocaine was dose-dependent and saturable at room temperature (fig. 1A, B) and on ice (data not shown). Scatchard analysis of the specific binding data on ice and at room temperature yielded K_d and B_{max} values of 169 (20) nmol $litre^{-1}$, 11.0 (1.6) pmol/mg protein and 153 (18) nmol $litre^{-1}$, 9.4 (1.6) pmol/mg protein, respectively. At the radioligand K_d specific binding was in excess of 50%. Unlabelled amethocaine 1 mmol $litre^{-1}$ was added to membranes labelled for 60 min at room temperature (fig. 1C) and 3 h on ice (data not shown) in an attempt to initiate ligand dissociation.

Table 1 pIC_{50} values (mean (SEM)) for local anaesthetic displacement of [^{3}H]amethocaine binding at room temperature to rat cerebrocortical membranes. *Determined by isotope dilution

Local anaesthetic	*n*	pIC_{50}	IC_{50}
Amethocaine*	11	6.89 (0.02)	129 nmol $litre^{-1}$
Procaine	7	5.20 (0.11)	6.3 μmol $litre^{-1}$
Lignocaine	7	3.46 (0.04)	347 μmol $litre^{-1}$
Prilocaine	6	2.81 (0.09)	1.5 mmol $litre^{-1}$
R(+)Ropivacaine	5	>4.00	>0.1 mmol $litre^{-1}$
S(−)Ropivacaine	5	>4.00	>0.1 mmol $litre^{-1}$
Bupivacaine	5	>3.00	>1 mmol $litre^{-1}$

Table 2 Effects of a range of ion channel blockers and neurotransmitters on [^{3}H]amethocaine binding to rat cerebrocortical membranes. Data are mean (SEM) percentage displacement at the maximum dose used

Ligand	Maximum dose used	*n*	% Displacement
Nifedipine	10^{-5}	6	0
Verapamil	10^{-5}	6	0
Diltiazem	10^{-5}	6	0
ω-conotoxin	3×10^{-7}	6	14.1 (3.0)
Tetrodotoxin	3×10^{-5}	6	0
Tetraethylammonium	10^{-3}	5	50.4 (1.9)
4-Aminopyridine	10^{-3}	6	75.0 (1.5)
L-glutamate	10^{-3}	6	0
MK801	10^{-4}	6	0
GABA	10^{-4}	6	0
Glycine	10^{-3}	6	0
Nicotine	10^{-3}	6	29.1 (2.6)

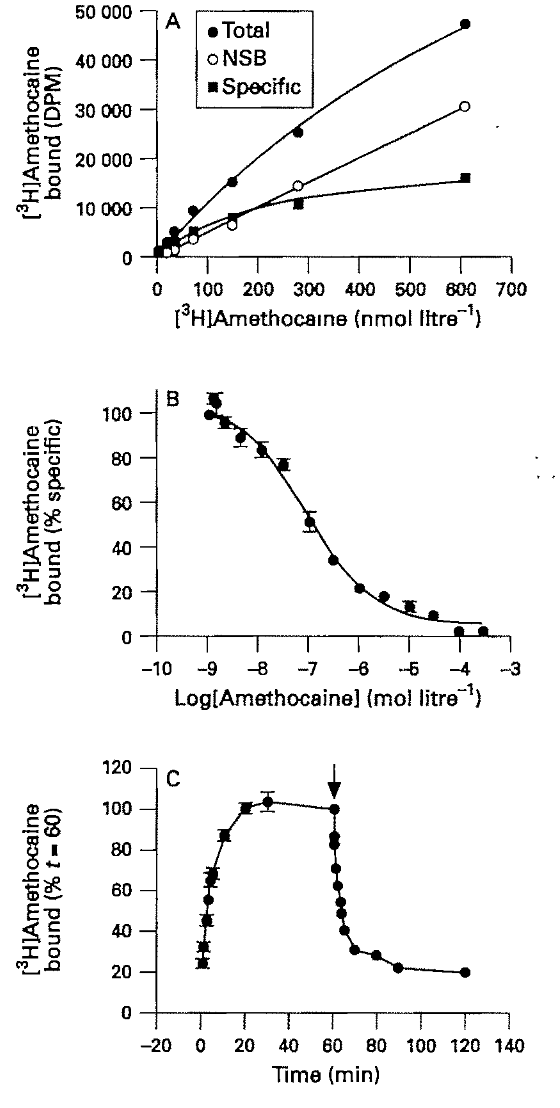

Figure 1 [^{3}H]Amethocaine binding (total, non-specific (NSB) and specific) to rat cerebrocortical membranes incubated at room temperature was dose-dependent and saturable (A) and displaced in a dose-dependent manner by unlabelled amethocaine (B). Association and dissociation time courses for [^{3}H]amethocaine (approximately 1 nmol $litre^{-1}$) binding are shown in (C). In (C), ligand dissociation was initiated by addition of excess unlabelled (1 mmol $litre^{-1}$, arrow) amethocaine and data are expressed relative to the t=60 time point normalized to 100%. Data are from a single representative experiment (from n=15) in (A), and mean (SEM) (n=11) in (B) and (n=6) in (C).

At room temperature, <20% of ligand had dissociated by 15 s and there was no appreciable dissociation on ice. Kinetic analysis yielded K_{ob} and K_{-1} values on ice and at room temperature of 0.023 min^{-1} and 0.001 min^{-1} (n=2) and 0.307 (0.026) min^{-1} and 0.299 (0.016) min^{-1} (n=6), respectively. As K_{ob} was so close numerically to K_{-1}, a dissociation constant value could not be calculated. In order to confirm the K_d value obtained in saturation studies, K_d was estimated in a series of isotope dilution studies where [^{3}H]amethocaine was displaced by unlabelled amethocaine (fig. 1B). pIC$_{50}$ (approximate K_d) values of 6.97 (0.05) (107 nmol litre^{-1}) and 6.89 (0.02) (129 nmol litre^{-1}) were obtained on ice and at room temperature, respectively.

A range of unlabelled local anaesthetics displaced [^{3}H]amethocaine binding in a dose-dependent manner, with pIC$_{50}$ values (as concentration of radiolabel was negligible compared with the K_d, IC$_{50}$ values are presented uncorrected for the competing mass of [^{3}H]amethocaine) shown in table 1. The rank order potency was amethocaine>procaine>lignocaine>prilocaine. Hill numbers for procaine, prilocaine and lignocaine were 0.65, 0.72 and 0.81, respectively, perhaps suggesting interaction with more than one site. However, these Hill numbers should be interpreted with caution because of the lack of complete displacement by these agents. Further discriminatory analyses were not performed. At bupivacaine 1 mmol litre^{-1}, R(+)ropivacaine 10^{-4} mol litre^{-1} and S(−)ropivacaine 10^{-4} mol litre^{-1}, 15.7 (1.7) %, 27.4 (1.5) % and 26.1 (1.0) % displacement was observed. There was no significant correlation between lipid solubility (measured as octanol:buffer partition coefficient[12]) and the pIC$_{50}$ for displacement of [^{3}H]amethocaine binding (r^2=0.47, P=0.31). Of the non-local anaesthetic agents tested, only 4-AP and tetraethylammonium produced greater than 50% displacement of specific binding with estimated pIC$_{50}$ values of 3.68 (0.02) (209 μmol litre^{-1}) and 3.07 (0.05) (851 μmol litre^{-1}), respectively (table 2).

Discussion

We have demonstrated dose-dependent and saturable binding of [^{3}H]amethocaine to rat cerebrocortical membranes. The binding was displaced by a range of unlabelled local anaesthetic agents but there was no correlation with lipid solubility, and bupivacaine and ropivacaine failed to produce 50% displacement at the maximum concentrations used. In addition, binding of [^{3}H]amethocaine was displaced by the K$^+$ channel blockers, 4-AP and tetraethylammonium.

The K_d values calculated by Scatchard analysis (153 nmol litre^{-1} at room temperature, 169 nmol litre^{-1} on ice) and by isotope dilution (129 nmol litre^{-1} at room temperature, 107 nmol litre^{-1} on ice) compare favourably with the values quoted by Grima and colleagues[13] and Reith, Kim and Lajtha[14] of approximately 170–180 nmol litre^{-1} in synaptosomes (an excitable preparation) analysed according to Scatchard.[11] B$_{max}$ values quoted in this study (approximately 13 pmol/mg protein) compare well with our data. In addition, Voight and Mannhold have reported binding of [^{3}H]lignocaine in a range of predominantly peripheral tissues concluding that the pharmacological significance of the binding site remains to be determined.[15] It should be noted that in these studies the emphasis was to examine binding to Na$^+$ channels rather than to use the radiolabelled local anaesthetic to examine "anaesthetic binding sites".

Binding of [^{3}H]amethocaine was displaced in a dose-dependent manner by amethocaine, procaine, lignocaine and prilocaine. There was no correlation between displacement of [^{3}H]amethocaine binding (pIC$_{50}$) and lipid solubility or anaesthetic potency. In addition, ropivacaine and bupivacaine produced only approximately 25% displacement at the highest doses used. The lack of an interaction with all local anaesthetic agents implies that the binding site for [^{3}H]amethocaine in rat cortical membranes does not represent a common target site for local anaesthesia. However, it is possible that if soluble, and available at higher concentrations, bupivacaine and ropivacaine may have been able to produce 50% displacement but the pIC$_{50}$ values would be very weak. In our study amino-ester local anaesthetics (amethocaine and procaine) displaced with highest affinity while amino-amide local anaesthetic agents (lignocaine, prilocaine, bupivacaine and ropivacaine) displaced with the weakest affinity.

L-channel (nifedipine, diltiazem and verapamil) and N-channel (ω-conotoxin) antagonists failed to displace [^{3}H]amethocaine from its binding site, implying a lack of interaction with L- and N-type voltage-sensitive Ca^{2+} channels. However, these studies report a lack of "direct" channel interaction and possibly the absence of an allosteric interaction between the displacer and [^{3}H]amethocaine binding sites. It is still conceivable that the displacing agent could interact at another binding site(s) not coupled to the [^{3}H]amethocaine binding site. Our previous study of the effects of local anaesthetic agents with [^{3}H]PN200-110 binding sites (L channels) showed a significant interaction but we did not examine if the interaction was allosteric.[9] However, Bolger and colleagues have shown such an allosteric interaction with [^{3}H]nitrendipine binding sites in rat brain and cardiac membranes.[5]

L-glutamate and MK801 (agents that interact with glutamate receptors), GABA, glycine and nicotine failed to displace [^{3}H]amethocaine binding. We were unable to displace [^{3}H]amethocaine binding with the Na$^+$ channel blocker, tetrodotoxin. This is in agreement with the work of Grima and colleagues[13] although they reported displacement with amiloride (and analogues), an agent that also binds to voltage-dependent Na$^+$ channels.[16 17] 4-AP and tetraethylammonium, agents that interact with K$^+$ channels, produced dose-dependent displacement of [^{3}H]amethocaine binding, which for 4-AP resulted in an IC$_{50}$ of approximately 209 μmol litre^{-1}. However, it is not possible to state that local anaesthetic agents interact with K$^+$ channels based on these data alone.

In summary, we have reported dose-dependent and saturable binding of [^{3}H]amethocaine to rat cerebrocortical membranes that was displaced in a dose-dependent manner by a range of unlabelled local anaesthetic agents. Amino-ester agents were more potent than amino-amide anaesthetics, perhaps implying that a single common binding site for all local anaesthetic agents is unlikely. There did not appear to be a direct interaction with known ligand binding sites on L- or N-type VSCC, GABA, glutamate, glycine or nicotinic receptors. Our data suggest a possible interaction with K^+ channels. However, at present, a non-specific binding site cannot be excluded.

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Dissociation between the effect of nitrous oxide on spontaneous and reflexly evoked sympathetic activity in dogs

D. MA, C. WANG, C. K. PAC-SOO, M. K. CHAKRABARTI AND J. G. WHITWAM

Summary

We have examined the effect of nitrous oxide on spontaneous sympathetic activity and Aδ- and C-fibre mediated somatosympathetic reflexes in renal nerves, evoked by supramaximal electrical stimulation of radial nerves in anaesthetized, paralysed dogs undergoing mechanical ventilation. In six preparations, nitrous oxide was administered at end-tidal concentrations of 10%, 30%, 50% and 70%, each for 20 min. Spontaneous renal sympathetic activity increased significantly to 147.8% and 151.2% of control values with 50% and 70% nitrous oxide, respectively (*P*<0.05), but there were no significant changes in Aδ and C reflexes We conclude that the large increase in spontaneous sympathetic activity was dissociated from somatosympathetic reflexes which remained unchanged at these concentrations of nitrous oxide. (*Br. J. Anaesth.* 1997; **79**: 525–529).

Key words
Anaesthetics gases, nitrous oxide. Nerve, somatic. Reflexes, sympathetic. Sympathetic nerve system. Dog.

Previously, several studies have demonstrated that nitrous oxide increases sympathetic outflow in both humans and animals. Indirect evidence of sympathetic activation, which has been summarized by Eisele,[1] obtained from volunteers breathing 40–60% nitrous oxide, is that it increases arterial pressure and heart rate,[2] cardiac output, plasma catecholamine concentrations,[2 3] systemic vascular resistance,[2 4] and causes pupillary dilatation[2] and sweating.[5] Direct evidence for sympatho-excitation by nitrous oxide has been studied by recording activity in sympathetic nerves in humans[6] and cats.[7] Although the effect of nitrous oxide on somatosympathetic reflexes has been observed in the cat,[8] it was studied at a concentration of only 75%, and there were no data for spontaneous sympathetic activity. Other studies have also used a limited range of concentrations,[6 7] and no previous study has attempted to relate the increase in spontaneous sympathetic activity with a possible effect on somatosympathetic reflexes. In this study we examined the effect of increasing concentrations of nitrous oxide on both spontaneous sympathetic activity and Aδ and C somatosympathetic reflexes.

Materials and methods

The study was approved by the UK Home Office (license PPL 90/00852). Six beagles, weighing 13.5–18 kg, were studied. Anaesthesia was induced with methohexitone 10–15 mg kg^{-1} i.v. and maintained using 1% α-chloralose in an initial bolus dose of 30 mg kg^{-1} followed by an infusion of 15–20 mg kg^{-1} h^{-1} i.v. The trachea was intubated and the lungs ventilated with oxygen-enriched air (HV 2000, SLE, Croydon, UK). Neuromuscular block was maintained with bolus doses of suxamethonium 10 mg i.v. every 30 min. An 18-gauge cannula was inserted into a cephalic vein in the right foreleg for drug and fluid administration. The left femoral artery was cannulated for recording arterial pressure and blood sampling. A Swan-Ganz catheter (American Edwards Laboratories) was inserted via the left femoral vein for measurement of cardiac output, central venous pressure (CVP), pulmonary arterial pressure (PAP) and pulmonary capillary wedge pressure (PCWP). Cardiac output was measured by thermodilution with a cardiac output computer (Com-1, American Edwards Laboratories). Oesophageal temperature was measured with a thermistor (Yellow Spring Instruments, OH, USA) and maintained at 37–39 °C with a heater built into the operating table. Arterial blood-gas tensions and pH_a were determined using a blood-gas analyser (Radiometer ABL 3, Copenhagen, Denmark); values were kept within limits (pH_a 7.30–7.40, arterial carbon dioxide partial pressure (Pa_{CO_2}) 4.8–5.3 kPa and arterial oxygen tension (Pa_{O_2}) 22.7–28.0 kPa) by adjusting ventilation and occasional administration of sodium bicarbonate. For each preparation, pH_a and blood-gas tensions were maintained close to control values during all relevant recordings. There were no significant changes in each preparation with only small differences in Pa_{CO_2} and pH_a between preparations; Pa_{O_2} was maintained above the chemoreceptor threshold (table 1). Arterial and venous pressures were measured with strain gauge transducers (Statham, Oxnard, CA). Heart rate was

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D. MA, MD, C. WANG, MB, PHD, C. K. PAC-SOO, MB, CHB, FRCA, M. K. CHAKRABARTI, BSC, MPHIL, J. G. WHITWAM, MB, CHB, PHD, FRCP, FRCA, Department of Anaesthesia, Royal Postgraduate Medical School, Hammersmith Hospital, Du Cane Road, London W12 0NN. Accepted for publication: May 16, 1997
Correspondence to D. M.

Table 1 Arterial pH and blood-gas tensions (mean (SD)) (n=6). No significant differences

	Control	10% N_2O	30% N_2O	50% N_2O	70% N_2O	Withdrawal
pH_a	7.371 (0.02)	7.359 (0.02)	7.359 (0.02)	7.367 (0.02)	7.376 (0.04)	7.396 (0.03)
Pa_{CO_2} (kPa)	4.9 (0.2)	4.8 (0.2)	4.9 (0.2)	4.7 (0.1)	4.9 (0.1)	4.8 (0.2)
Pa_{O_2} (kPa)	26.2 (1.9)	26.9 (2.6)	26.0 (2.2)	26.5 (3.1)	26.0 (3.1)	26.0 (3.6)

obtained from the arterial pulse wave. All haemodynamic signals were amplified, displayed on a monitor and stored on disk for later analysis (Maclab Software, AD Instruments Pty Ltd, Australia). Systemic (SVR) and pulmonary (PVR) vascular resistances were calculated using standard formulae (SVR=(MAP−CVP)×80÷CO, PVR=(PAP−PCWP)×80÷CO).

ELECTROPHYSIOLOGY

Surgical procedures

After setting up, the preparation was placed and maintained in the left lateral position. The lateral branch of the superficial branch of the radial nerve was exposed in the left foreleg, desheathed and cut distally, and mounted on silver–silver chloride electrodes in a pool of mineral oil for electrical stimulation. The renal sympathetic nerves were exposed retroperitoneally alongside the renal artery; a single fascicle was desheathed, cut distally near the kidney, immersed in a mineral oil pool and mounted on silver–silver chloride electrodes for recording sympathetic activity.

Electroneurogram and signal processing

Efferent activity in renal sympathetic nerves was processed through a pre-amplifier (Tektronix type 122) and displayed on a dual-beam oscilloscope (Tektronix type 565). Supramaximal electrical stimuli (frequency 0.33 Hz, intensity 30 V, duration 0.5 ms) were applied to the radial nerve by a stimulator (S88, Grass, Quincy, MA). Evoked somatosympathetic responses recorded in renal sympathetic nerves were averaged (16 responses), rectified and integrated using a neurolog system (NL 90, Welwyn Garden, UK). Both amplified and integrated signals were displayed on an oscilloscope and hard copy was recorded with a thermal system (Gould 1602, Essex, UK). For spontaneous sympathetic activity, the signal was subjected to full-wave rectification and then integrated with a time constant of 100 ms (Neurolog NL 90). The total electrical activity in the integrated signals of evoked sympathetic reflexes, and spontaneous sympathetic activity during 20-s periods was measured in arbitrary units. Data were based on the average of three measurements at each point in each preparation and subsequently expressed as a percentage of control values.

ADMINISTRATION OF NITROUS OXIDE

The preparation was allowed to stabilize for at least 1 h after completion of surgery, before control measurements were obtained. Nitrous oxide was then administered to each of six preparations at 10%, 30%, 50% and 70% (expired end-tidal concentration) for 20 min, while maintaining $P\text{E}'_{O_2}$ at approximately 30% and Pa_{O_2} relatively constant above the chemoreceptor threshold; Pa_{CO_2} and pH_a were maintained at control values and adjusted when necessary before each data set was recorded (table 1). Expired concentrations of nitrous oxide were measured by a Datex Capnomac II, which was calibrated before each experiment with standard gas (Quick Cal, Datex Division of Instrumentarium Corp., Helsinki, Finland). Equilibrium end-tidal concentrations were used to compare the effect of changes in the concentration of nitrous oxide on evoked reflexes and spontaneous sympathetic activity. After initial control readings, measurements were repeated to obtain subsequent values towards the end of each 20-min period of nitrous oxide administration, immediately before the 5-min period of stimulation of the radial nerve necessary to produce a complete data set. Measurements were also repeated 1 h after withdrawal of nitrous oxide.

STATISTICAL ANALYSIS

All data are expressed as mean (SD). Statistical analysis was performed by analysis of variance (ANOVA) followed, where this showed significant differences ($P<0.05$), by paired t tests. Differences were considered statistically significant when $P<0.05$.

Results

SYMPATHETIC ACTIVITY

Figure 1 shows typical recordings of spontaneous sympathetic activity and Aδ- and C-fibre mediated somatosympathetic reflexes, evoked by supramaximal electrical stimulation of the radial nerve.

Mean spontaneous sympathetic activity increased to 111.9% of control values (ns) at 30% nitrous oxide and subsequently increased significantly to 147.8% and 151.2% of control values at 50% and 70% end-tidal concentrations of nitrous oxide, respectively ($P<0.05$). It remained at 112.4% of control values 1 h after nitrous oxide withdrawal but this difference was not statistically significant (fig. 2A).

There were no significant changes in Aδ and C reflexes throughout the study (fig. 2B).

HAEMODYNAMIC DATA

There were no significant changes in heart rate (HR) or mean arterial pressure (MAP) in the absence of

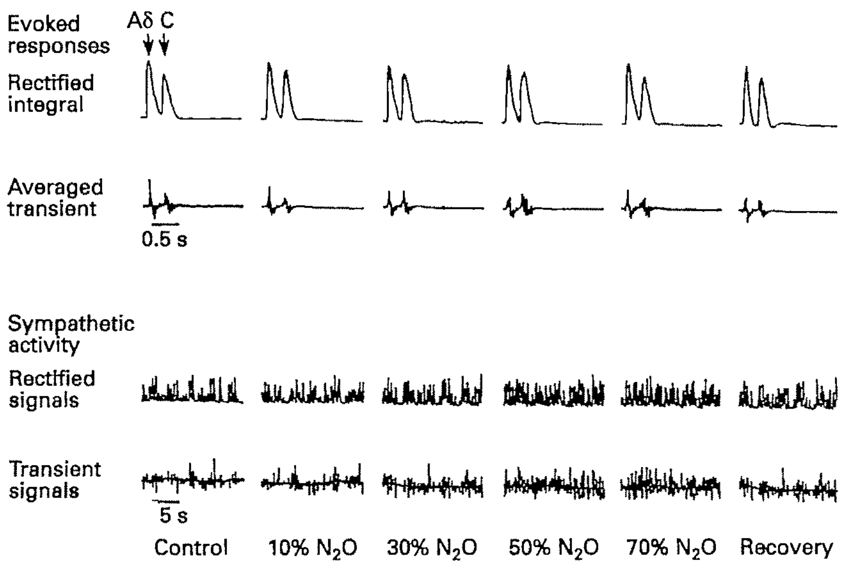

Figure 1 Data from one preparation showing the effect of nitrous oxide (N_2O) on spontaneous sympathetic activity, Aδ responses (early) and C responses (late). Top pair of traces—evoked responses: lower traces are averaged responses of Aδ and C reflexes (×16); upper traces are rectified and integrated signals. Bottom pair of traces—spontaneous sympathetic activity: lower traces are directly recorded activity, upper traces are rectified and integrated signals.

electrical stimulation of the radial nerve (fig. 3). There were small increases in HR and MAP during stimulation of the radial nerve but only some of the changes in MAP reached statistical significance ($P<0.05$).

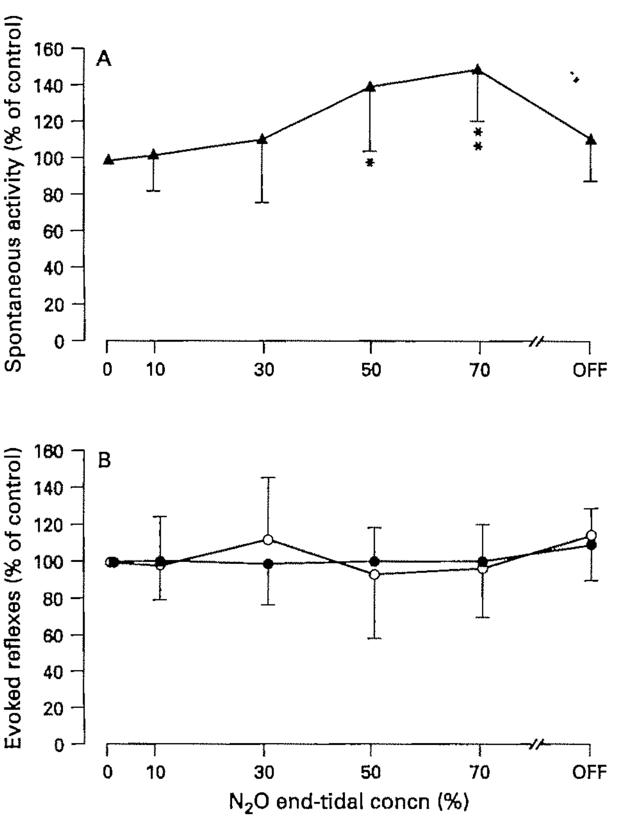

Figure 2 Effect of increasing concentration of nitrous oxide (N_2O) on (A) spontaneous renal sympathetic activity and (B) Aδ- and C-fibre mediated somatosympathetic responses evoked by supramaximal electrical stimulation of the radial nerves (mean (SD)) ($n=6$). ○=C-fibre responses; ●=Aδ-fibre responses. $^*P<0.05$; $^{**}P<0.01$ compared with control. There were no significant changes in Aδ and C reflexes throughout the study.

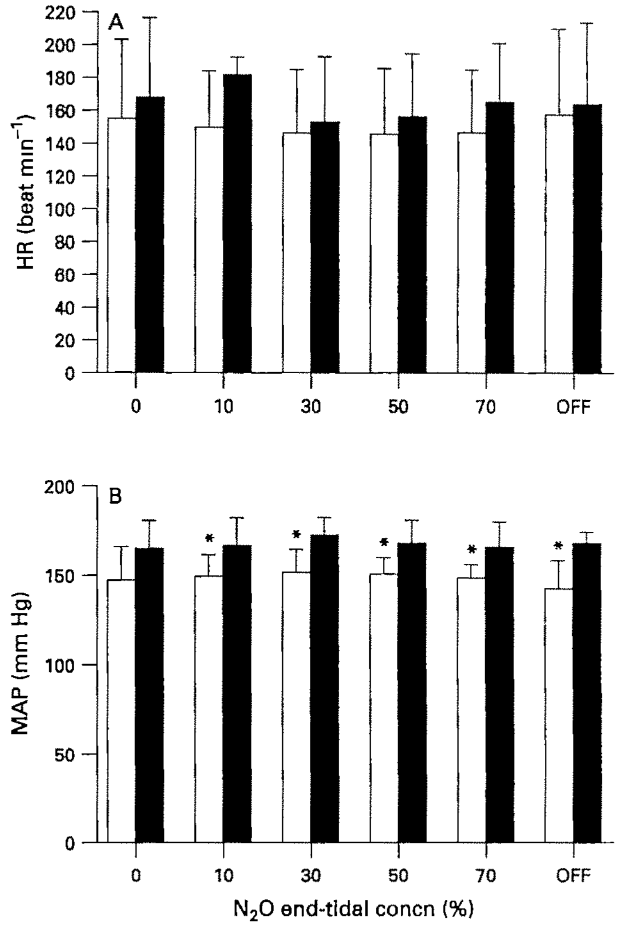

Figure 3 Changes in heart rate (HR) (A) and mean arterial pressure (MAP) (B) before (☐) and during (■) stimulation of the radial nerve at each concentration of nitrous oxide (N_2O) from 10% to 70% (mean (SD)) ($n=6$). $^*P<0.05$ for comparison between non-stimulated and stimulated values at each concentration of nitrous oxide. There were no significant differences compared with control.

Although mean cardiac output gradually increased to 1.85, 1.86, 1.87 and 1.91 litre min^{-1} from the control value of 1.71 litre min^{-1} after 10%, 30%, 50% and 70% nitrous oxide, respectively, this was not statistically significant, and returned to control after its withdrawal.

In this small number of animals there were no significant changes in SVR, PVR, CVP or PCWP.

Discussion

This is the first direct evidence of sympatho-excitation produced by nitrous oxide in a concentration-related manner, and also the first study combining data of its effect on spontaneous sympathetic activity and Aδ and C somatosympathetic reflexes. There were two main findings: nitrous oxide caused an increase in sympathetic activity which showed a sigmoidal relationship to increasing concentrations and which reached a maximum of approximately 50% at a concentration of 70% nitrous oxide; there was no significant change in Aδ- and C-fibre mediated somatosympathetic reflexes in response to administration.

Sympathetic outflow increases in response to hypotension and low venous pressure with low atrial pressures, because of baroreflexes, and an increase in Pa_{CO_2} or a low Pa_{O_2}. However, hypotension and low CVP did not occur during these experiments, Pa_{O_2} was maintained above the chemoreceptor threshold[9] and Pa_{CO_2} and pH_a near control values (table 1).Therefore, the increase in spontaneous sympathetic activity cannot be attributed to any of these physiological variables and was a reproducible response to nitrous oxide. We also considered the possibility that the periods of nerve stimulation could be a cumulative factor increasing spontaneous sympathetic activity. However, it was observed in pilot studies that spontaneous sympathetic activity always returned to control levels within approximately 5 min of ceasing stimulation, which confirmed many years' experience with a variety of experiments using similar preparations. Smith and colleagues reported that the addition of nitrous oxide to halothane–oxygen anaesthesia in humans produced vasoconstriction, increased oesophageal temperature and dilated the pupils.[2] Fukunaga and Epstein, using direct recordings of splanchnic nerve activity in cats anaesthetized with 0.9% halothane, found an increase of 13% in sympathetic activity after addition of 70% nitrous oxide to the inspired gas; they suggested that the increase in sympathetic activity produced by nitrous oxide was mediated centrally and caused by effects on neurones in suprapontine structures.[7] Ebert and Kampine reported that brief exposure to nitrous oxide in healthy volunteers caused an increase in efferent activity in sympathetic nerve fibres in the peroneal nerve innervating skeletal muscle.[6] Sellgren, Pontén and Wallin showed that in patients, nitrous oxide was associated with an increase in sympathetic activity in muscle nerves, which was obtunded by isoflurane in a concentration-dependent manner,[10] while Ebert reported that 40% nitrous oxide in human volunteers produced augmentation of baseline sympathetic nerve activity in nerves supplying skeletal muscles.[11] All of these observations are in keeping with the results of our study. The increase in sympathetic activity produced by nitrous oxide may be responsible in part for the relatively stable cardiovascular effects noted when it is administered together with other anaesthetic agents which depress the sympathetic nervous system. It represents a positive contribution to the critical debate for its continued use in some patients not only because of sympatho-excitation but also by allowing a reduction in the requirements of additional agents and drugs. However, its use in patients with cardiac disease or in those with endocrine disorders requires careful consideration.

The mechanism for central sympatho-excitation during nitrous oxide administration is unknown, and clearly an increase in excitatory neurotransmitters could provide an explanation. However, in decerebrate cats exposed to nitrous oxide, preganglionic splanchnic sympathetic activity is decreased rather than increased,[7] and hence the effect of nitrous oxide could be a result of depression of central inhibitory areas. It is interesting that in the last century nitrous oxide was originally regarded as an stimulant of the central nervous system, and only later were its analgesic properties appreciated.[12]

Nociceptive stimulation of afferent somatic sensory nerves causes changes in systemic arterial pressure and heart rate, which are mediated by the autonomic nervous system.[13] Directly recorded sympathetic responses to single supramaximal electrical stimuli applied to a somatic nerve show two bursts of activity, termed somatosympathetic reflexes, and are mediated by afferent Aδ and C fibres.[14] This study demonstrated clearly that nitrous oxide did not depress somatosympathetic reflexes at the concentrations used. Although it has been suggested that endogenous opioids are involved in its analgesic effects,[15] not all studies support this view.[16] It was suggested that nitrous oxide has little effect on the firing rate of dorsal horn neurones,[17] and Komatsu and colleagues[18] reported that the analgesic action of nitrous oxide can be attributed to activation of a descending supraspinal pain inhibition system. The MAC for nitrous oxide in the dog is equivalent to 188%,[19] and hence it would not be expected to suppress somatosympathetic reflexes except under hyperbaric conditions. However, Ogawa and colleagues[8] reported that a "late" reflex potential evoked by electrical stimulation of the femoral nerve was depressed by inhalation of 75% nitrous oxide in oxygen in cats, which has not been confirmed in our study in the dog.

It could be postulated that sympatho-excitation by nitrous oxide would enhance nociceptive somatosympathetic reflexes. Alternatively, when the sympathetic nervous system is already highly active, nociceptive stimulation may fail to induce further spatial or temporal summation and hence excitation within a rhythmically repetitively depolarized pool of sympathetic neurones, and because of such occlusion, the evoked responses could be depressed below control values. As neither occurs, the term dissociation was applied to the relative effects of nitrous oxide on spontaneous and evoked sympathetic activity.

In summary, by causing increases of up to 50% in spontaneous sympathetic activity, nitrous oxide provides the greatest central stimulus to the sympathetic system of all inhalation agents so far described and its effect is concentration dependent. In contrast, at 70% concentration it has no effect on Aδ- and C-fibre mediated somatosympathetic reflexes, in spite of a high level of spontaneous sympathetic excitation, indicating dissociation of its effects.

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REVIEW ARTICLE

Anaesthesia for the surgery of emphysema

I. D. CONACHER

Thoracic anaesthesia is now established in a third age. The first age related to surgery for infective conditions, predominantly tuberculosis, the second was defined by surgery for bronchogenic cancer and the third is surgery for respiratory failure. The anaesthetic imperatives of this latest age are epitomized by emphysema, with some variants treated with lung transplantation and, recently, surgery for the oxymoron, lung volume reduction.

Small areas of emphysematous changes are common in the general population, occasionally resulting in pneumothoraces; a significant number of these patients require surgical intervention. The presence of large cystic areas or bullae, and bilateral, widespread diffuse areas of enlarged air spaces distal to terminal bronchioles[32] are much rarer and their management fraught with risk. Until the advent of lung volume reduction surgery, the anaesthetic literature was sparse, with mostly case reports and series involving small numbers. Personal experience of managing cases with moderate to severe respiratory failure, as a result of end-stage emphysematous disease, serves as an illustrative framework (table 1) and has much to teach about the dangers, how anaesthesia may contribute to morbidity and mortality, and where risks can be reduced.

An early specimen of emphysema, purportedly the lung of Dr Samuel Johnson, is illustrated in Mathew Baillie's *The Morbid Anatomy of Some of the Most Important Parts of the Human Body* (London, Bulmer, 1812).[47] Laennec[42] described the clinical condition of dyspnoea, cyanosis, dry cough, over-inflated chest, cardiac hypertrophy and quiet respiratory sounds on auscultation. He recognized the continuum from the small areas of enlarged air cells, illustrated in his book, to the giant cyst or bulla. He foresaw pathognomonic features now so often seen on chest x-rays and CT scans,[74] noting that: "When this disease occupies only one side, or exists much more in one lung than the other, this side is evidently enlarged, and the intercostal spaces wider...........and instead of its natural compressed shape it (the chest) exhibits an almost rounded or globular outline".[42]

John Snow[22] had an interest in the condition and recorded its occurrence in some of his patients. A particular danger of anaesthesia was noted 100 yr later: "A dangerous state of affairs may exist in the rare case of a cyst, usually large, of the lung, communicating with a bronchus. The communication is often valvular so that on inflation the cyst is distended without reduction in size during deflation. Compression of the surrounding lung occurs. If the condition is unsuspected by the anaesthetist, the more energetic his attempts at resuscitation by inflation, the more the lungs are collapsed by increasing distension of the cyst. Rapid asphyxia and death of the patient results unless the chest is quickly opened and the lungs allowed to expand".[51]

This classic description of the "*breath stacking*" and "*pulmonary tamponade*" effect of positive pressure ventilation and of over enthusiastic resuscitation is as true today as it was 40 yr ago. However, opening the chest rapidly would not be regarded as a modern first aid measure, although if occurring on induction of anaesthesia such a manoeuvre may be considered.[5] Deliberate decompression of bullae with intercostal drains remains an option, particularly to pre-empt the development of tension pneumothorax during anaesthesia.[20]

Surgery of bullae and diffuse emphysema

There are occasional reports of operations being conducted for bullae before the Second World War[31] but it was only when manifestations were gross that surgery was an option. Belcher described 90 patients with large bullae on whom he had operated since the early 1950s.[2] There was a 12% operative mortality rate and at follow-up, in some cases 10 yr after surgery, 35% had died but more than 50% had demonstrably improved. Hugh-Jones, Ritchie and Dollery[33] reported a 10% operative mortality rate. From then on, a variety of surgical options for obliteration of bullae were described; some, based on physiological misconceptions, were bizarre. Segmental resection,[29] lobectomy,[87] plication[3] and local excision[85] were suggested as suitable techniques for selected cases with well localized lesions of various sizes. Tracheostomy,

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Key words
Surgery, thoracic. Complications, emphysema. Complications, barotrauma. Lung, respiratory failure. Lung, volume. Lung, transplantation.

I. D. CONACHER, FRCA, MD, FRCP (ED), Cardiothoracic Centre, Freeman Hospitals NHS Trust, Freeman Rd, Newcastle upon Tyne, NE7 7DN.

Table 1 Index and illustrative cases. ()*Predicted values. T_LCO=CO transfer factor (mmol min^{-1} kPa^{-1})

Patient No.	Sex	Age (yr)	Diagnosis	Surgery	Access	FEV$_1$ ()*	FVC ()*	TLC ()*	RV ()*	T_LCO ()*	KCO (mmol min^{-1} kPa^{-1}) ()*
1	M	61	Bilateral apical bullae	Apical bullectomy, plication	Thoracotomy	0.55 (3.25)	1.65 (4.40)	9.35 (6.95)	7.7 (2.35)	2.65 (9.4)	0.68 (1.37)
2	F	47	α_1-Antitrypsin deficiency	Single lung transplant	Thoracotomy	0.55 (2.30)	2.2 (2.75)	8.3 (4.30)	6.05 (1.50)	1.45 (5.81)	0.42 (1.56)
3	M	52	Left lower lobe bulla	Bullectomy	Thoracotomy	0.89	1.75	7.65	5.88		1.67
4	M	43	Idiopathic bullous emphysema	Bilateral bullectomy	Sternotomy	0.70 (4.20)	1.40 (5.35)	9.55 (7.45)	7.70 (2.05)	5.12 (11.4)	1.54 (1.63)
5	F	46	Idiopathic bullous emphysema	Volume reduction	Sternotomy	0.20	0.89	10.25 (4.35)	9.1 (1.65)		
6	F	47	Idiopathic bullous emphysema	Volume reduction	Sternotomy	0.30 (2.65)	1.30 (3.20)	7.05 (4.95)	5.75 (1.70)	2.25 (8.37)	0.53 (1.53)
7	M	49	Asthmatic. Bulla	Bullectomy	Thoracotomy	0.75 (3.80)	2.80 (4.95)	7.35 (4.55)	4.55	5.0 (11.1)	1.01 (1.5)
8	F	48	α_1-Antitrypsin deficiency	Single lung transplant	Thoracotomy	0.45 (2.60)	1.15 (3.15)	7.1 (4.9)	5.95 (1.70)		
9	M	49	α_1-Antitrypsin deficiency	Single lung transplant	Thoracotomy	0.65 (3.65)	4.40 (4.70)	11.85 (6.95)	7.45 (2.15)		

autonomic denervation, pneumoperitoneum, costochondrectomy, thoracoplasty, tracheal stenting and intracavity suction and drainage[44] have had their advocates.[1 19 57] In the latter, a forerunner of minimal access surgical techniques, the reported operative mortality rate was 6.5%. Recently, laser and videoscopic technology have been used to ablate small bullae.[84]

In 1959, Brantigan, Mueller and Kress[6] reported on the surgical management of diffuse emphysema but a high mortality (18%)[68] dissuaded many from surgical options until the advent of transplantation. For generalized conditions, such as α_1-antitrypsin deficiency, single lung transplantation was used, initially with little success,[83] but with advances in transplantation, single,[14 37] double[66] and heart–lung transplants[5] are all now practised with satisfactory results. From the experience has come the realization that some of the benefit is mechanical rather than physiological. The smaller functional residual capacity (FRC) of the transplant enables chest wall and diaphragm dynamics to improve so that function is more efficient. This is the basis of a resurgence in interest in early surgical options for diffuse bullous emphysema, such as lung volume reduction, which uses techniques and lessons from transplantation, new technologies (lasers and thoracoscopes), and modern suturing, stapling and buttressing materials.[16 24 75] The original premise was that reducing lung volume would improve elastic recoil and exercise circumferential traction on small airways, reducing the propensity for air trapping.[6] The main reason for success is improved airflow[17] and more efficient chest wall and diaphragm mechanics, as suggested originally.[6] But other factors that may be relevant are recruitment of alveoli compressed by bullae and improvement in ventilation–perfusion matching resulting from reduced pulmonary vascular resistance, improved right ventricular performance and greater venous return consequent on reduction of mean intrathoracic pressure.[71 88] There is evidence that improvement is rapid, within hours of surgery.[80 81]

Hard lessons of experience

Two cases (table 1) serve as illustrations of how the anaesthetic and surgical process can be particularly hazardous and set off a train of events that ultimately may be fatal.

CASE NO. 1

A 47-yr-old female with bilateral emphysema secondary to α_1-antitrypsin deficiency was undergoing a right single lung transplant. After induction of anaesthesia, a double-lumen tube was inserted. The procedure was uneventful until the start of one-lung ventilation. A bulla, or some bullae, became over inflated. Hyperinflation occurred impeding venous return. Barotrauma progressing to bilateral pneumothorax, pneumopericardium and pneumoperitoneum followed in rapid succession and despite commencement of cardiopulmonary bypass, venous return remained poor, hypoxaemia increased and death occurred.[13]

CASE NO. 2

A 61-yr-old male, house bound, with large bilateral apical bullae and a march tolerance of 10 yards, was anaesthetized for plication of a left apical bulla using conventional (for the time, 1981) one-lung anaesthesia. "*The bulla was twisted and obliterated and then multiple ligatures were placed round the resulting cord of tissue. The same was done to one smaller bulla in the upper lobe........The lung was then re-inflated and it was noted that a large bulla appeared spontaneously in the lower lobe.*" (operation note). The trachea was extubated and the patient returned to recovery. Two hours later he was comatose with a pH of 7.07, Pa_{CO_2} of 12.0 kPa and Pa_{O_2} of 10.6 kPa while receiving 40% oxygen. He was resuscitated and his trachea re-intubated for a short time before being extubated with an infusion of doxapram and low-dose ketamine for analgesia. His condition deteriorated overnight and intermittent positive pressure ventilation was commenced. A large air leak occurred from the left lung which in due course collapsed. A bulla in the right lung began to expand and mediastinal shift to the left occurred. A double-lumen tracheal tube was inserted. Asynchronous independent lung ventilation was started with resolution of some of the problems of the right lung but an increase in the left-sided air leak. Progressive circulatory and organ deterioration occurred culminating in the patient's death.

Case No. 1 illustrates the effects of induction of anaesthesia in instituting unnatural pressures and forces that can lead to haemodynamic collapse, volutrauma and barotrauma. Air from alveolar rupture tracked in a malignant manner, in the same way that was demonstrated more than 50 yr ago[46] and more recently reported in patients undergoing artificial ventilation and with adult respiratory distress syndrome.[86] Case No. 2 also illustrates the problems of applying supranormal airway pressures to damaged lung weakened by surgery, the longer term problems of providing adequate analgesia for the self-ventilating patient and the consequences of prolonged air leak. The latter is the main cause of postoperative morbidity[57] and predisposes to infection, marasmus and multiple organ failure.

Anaesthetic assessment

The anaesthetist should be aware that postoperative progress is an ordeal, particularly if air leaks develop. For patients to maintain self-ventilation for as long as possible implies that effort must be sustained at considerable expense to energy reserves. Adequate nutritional status, with implementation of enteral and parenteral supplementation if necessary, to reduce the cachectic state of many sufferers of emphysema is seen as an important part of the rehabilitation programmes to which many institutions subject potential lung transplant recipients and those undergoing lung volume reduction.[7]

Non-invasive assessment of right ventricular function[18] is important as pulmonary vascular resistance almost certainly increases during anaesthesia, application of positive pressure ventilation and commencement of one-lung ventilation.[59 60]

The quality of lung that is to function for gas exchange is paramount. Bullae, even "giant" in nature, may constitute little hazard as the affected lung can be isolated and routine one-lung ventilation conducted (case No. 3, fig. 1) on the contralateral one. But, as it is now common, particularly for diffuse disease, to operate on both lungs[4 15 35] (case No. 4) it is necessary to examine both lung fields from the perspective of having to alternate the lung to be used for gas exchange, ventilation and anaesthesia during surgery. One concomitant risk factor is obstructive airways disease.[77] The presence of widely dispersed non-homogeneous and diffuse pathology is particularly hazardous as each cystic area functions differently, has different pressure–volume and time constants, and different resistance to positive pressure generated by externally applied positive pressure or auto-generated by gas trapping.[26 27 40 64 73 78] Most of the relevant information for predicting the patient at high risk can be obtained from the chest x-ray, CT scan of the chest and ventilation–perfusion scans.[49] These investigations aid decisions to the most suitable method of achieving one-lung ventilation and whether or not selective bronchial blocking is likely to be of value. Assessing the state of the non-bullous lung fields is regarded as important to define the population most likely to benefit from radical surgery; for this, regional pulmonary function tests, such as dynamic ventilation volume using ^{133}Xe washout studies,[56] are recommended .

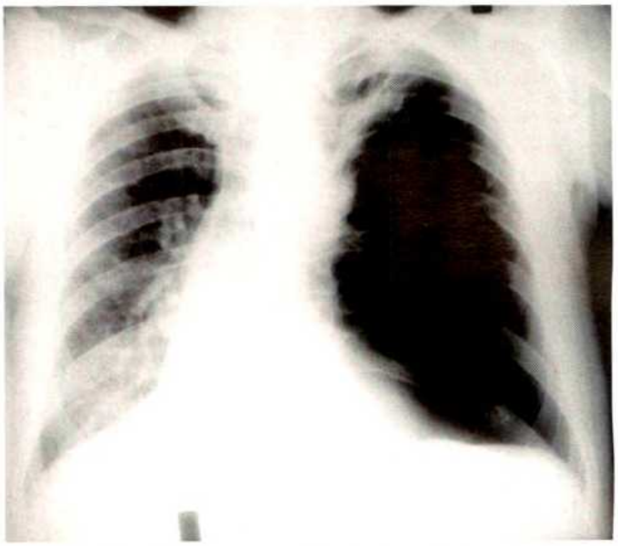

Figure 1 PA chest, case No 3. Left lower lobe bulla. Left lung isolated with a double-lumen tube. Bullectomy enabled re-expansion of compressed left upper lobe.

From the anaesthetic perspective, classification of bullae, traditionally[17] or according to surgical criteria,[84] is of little value as all types and sizes are prone to gas trapping phenomena. There is more value in a concept of clinically pathophysiological sub-groupings such as those friable enough to rupture and precipitate a tension pneumothorax before the chest is open, and those in which the feeding bronchus is dysfunctional and acts as a valve which precipitates hyperinflation after opening. The latter has subsets (a PEEP-dangerous subgroup and a PEEP-therapeutic subgroup) where an artificial expiratory resistance (PEEP$_e$) prevents the valvular mechanism becoming operational. There are few investigative or clinical indicators to these pathophysiological subsets, except the experience gained from trial and error with various ventilation techniques. There is no substitute for an expectant policy of gas trapping phenomena developing.

Anticipated predictors of poor outcome from surgery, such as those patients presenting with hypoxaemia and carbon dioxide retention (case No. 5) and those who fail to complete rehabilitation programmes, have in practice proved unreliable.[1] Measurement of intrinsic positive end-expiratory pressure (PEEP$_i$) is thought to be a predictor of outcome of lung volume reduction.[80] This index of air trapping is a potentially valuable measurement for the anaesthetist in the preoperative assessment of patients, indicating those most likely to suffer if further increases in intrathoracic pressure occur as a result of the anaesthetic process and aiding in decisions of the appropriateness and most therapeutic level of extrinsic PEEP ($PEEP_e$).[76]

Pre-induction of anaesthesia

There are no hard and fast rules to premedication.[7] Personal preference remains morphine and atropine premedication, as the antisialogogue element makes insertion of bronchoscopes and tracheal tubes less messy. Steroids and other bronchodilators have commonly been used; supplementation may be regarded as necessary at this phase.[7]

Patients should be prepared in the anaesthetic room as for a major case, with good venous access, invasive monitoring of arterial pressure from radial artery cannulation and central venous access. It should be borne in mind that the apices of the lung are vulnerable to needle punctures close to the traditional sites of large vein access and for this reason central venous access is safer from the antecubital fossae rather than neck or subclavicular approaches. With the various forms of lung transplantation, the requirement for cardiopulmonary bypass[18] dictates the level of monitoring but there should be a cautious and conservative attitude to the use of pulmonary flotation catheters, and indications for use are in those with concomitant left ventricular dysfunction[7 79] or in whom pulmonary hypertension is regarded as a potential problem.[5]

Pain relief must be optimal as soon as possible as it enables early tracheal extubation and rapid return to self-ventilation, regarded as crucial to the recovery of patients undergoing lung volume reduction. Those with pioneering experience regard it as so vital that extradural catheters are sited under fluoroscopic control to guarantee correct placement.[79] Personal preference is to site the extradural catheter in the seated conscious patient before induction of anaesthesia (case No. 6). High sites (T3–4) are advocated,[79] and with the patient sitting upright, needle insertion is at a comfortable height for the standing operator. At this level, in this position, the spinous processes are almost horizontal, making a midline approach to the extradural space easier. Other groups have found satisfactory analgesia from lumbar-placed catheters[34] after surgery.[5]

Most UK units (personal survey) use opioid and low-dose bupivacaine combinations, often with a patient-controlled mode to maintain analgesia during recovery. But it is a measure of how crucial is the extradural to the success of lung volume reduction surgery that some units recommend omitting the opioid component of extradural infusions because of the risk of nausea and vomiting.[79]

Induction of anaesthesia

In 1953, Mushin and Rendell-Baker,[51] reporting on the early experience of anaesthetizing patients with lung cysts, stated: "In these cases the need for inflation of the lungs should be carefully avoided until the chest is opened; relaxants and respiratory depressants are therefore contraindicated during induction of anaesthesia".

Elements of this statement remain true, based as it is on a premise that the safest levels of intrathoracic pressure are those during spontaneous, and unassisted, respiration and close to a negative mean. This concept underpins the general philosophy that patients who have undergone surgery for emphysematous conditions are safest breathing spontaneously as rapidly as possible after the procedure and the trachea should be extubated as early as possible. Neuromuscular blocking agents and respiratory depressant drugs are no longer regarded as contraindicated[7] but in view of the requirement for rapid antagonism, they should be pharmacologically specific and short acting. These enable optimum conditions for intubation with double-lumen tubes and suppress spontaneous respiratory activity, coughing and diaphragmatic activity which interfere with surgery. Atracurium, vecuronium, fentanyl and alfentanil are the current agents of choice, preceded by an induction dose of propofol which, with modern infusor systems, can be continued for maintenance of anaesthesia.

Hasenbos and Gielen[28] recommended a spontaneously breathing induction technique and double-lumen tracheal intubation under sedation and local anaesthetic for cases of giant bullae (case No. 7, fig. 2) and Myles and Moloney[53] used the technique to induce anaesthesia in a patient with a large air leak from a bulla. Further increases in the severity of disease of those undergoing operation, however, imply that even a coughing fit, for instance from maladroit administration of local anaesthesia to the larynx and trachea,[7] may precipitate the development of dynamic hyperinflation. Evidence is anecdotal, but the availability of sevoflurane will impact on some traditional reservations against gaseous induction in patients with sensitive and reactive airways. Conditions for safe intubation and positioning of double-lumen tubes can be achieved by induction of anaesthesia with etomidate or

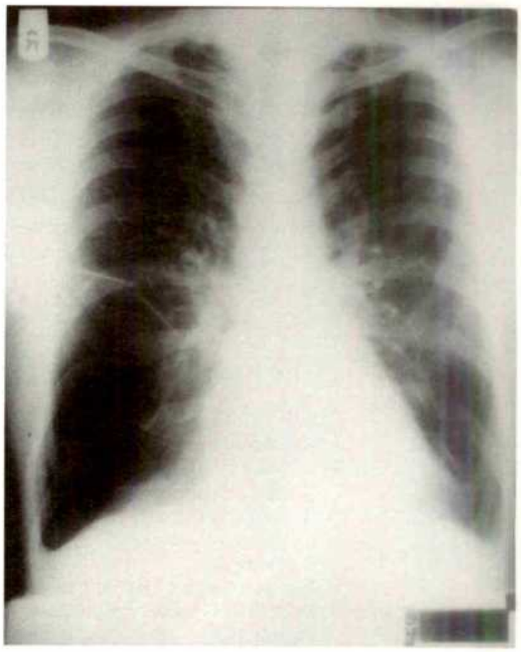

Figure 2 PA chest, case No 7. Right lower lobe bulla. Generalized emphysematous changes in both lung fields. High risk of gas trapping. Gas induction of anaesthesia.

propofol, short-acting opioids and non-depolarizing neuromuscular blocking agents, but it is essential that manual ventilation is commenced cautiously, with small tidal volumes, low inspiratory pressures and deliberate prolonged expiratory phases to atmosphere.[5 10] With such manoeuvres, hypoxaemia and hypotension have been avoided during induction of anaesthesia, and although carbon dioxide retention occurs, this is only to levels regarded as permissive.[5 65] The combined use of general anaesthetic and laryngotracheal local anaesthesia for intubation has been advocated and would seem worth considering, particularly for those with co-existent cardiac disease, to suppress the pressor effects of intubation, or in those patients in which isolation of a bulla from the ventilation system is a prerequisite.[58]

Control of the airway

A form of airway management that separates the lungs is mandatory. This is achieved most easily with a double-lumen tracheal tube but the Univent tube[38] has proved useful.[69] Double-lumen tubes add flexibility; lungs can be collapsed and expanded at will for surgical convenience; in the event of gas exchange problems, recruitment of the other lung is facilitated; and each lung can be ventilated and supported independently. For isolated left-sided lesions, an endobronchial blocker or a right-sided double-lumen tube can be inserted. For bilateral procedures, which encompass most lung volume reduction and sequential single lung transplantations, left-sided tubes should be used as the long main bronchus ensures more reliable lung separation and mitigates for bronchus leaks that impede surgery.

Maintenance of anaesthesia

Of the i.v. agents, propofol is the mostly recently advocated[10 39] supplanting agents such as gamma OH,[28] Althesin[58] and ketamine,[45] which were considered previously to have properties appropriate to the management of these physiologically unstable patients (in a climate where volatile agents were regarded as contraindicated because of effects on hypoxic pulmonary vasoconstriction).

There is no place for nitrous oxide; not only does it transfer into the air filled spaces[21 50] increasing intra-alveolar pressure with consequent effects on pulmonary capillary blood flow, but it also causes an increase in pulmonary vascular resistance.[70] However, volatile agents do have a place. I find them particularly useful when the chest is closed and the operation is ending. Neuromuscular block is antagonized as soon as the chest wall is sealed and the patient allowed to breathe spontaneously with oxygen and either enflurane or isoflurane. If ventilation is judged adequate, based on tidal ventilation, rate and effort, inspired oxygen is reduced gradually by introduction of an increasing concentration of air. In this way the potential for early extubation can be judged. Oxygenation status and haemodynamic variables remain the touchstones when the lungs are not visible. Some carbon dioxide retention causes no harm, providing oxygenation is maintained at safe levels.[5 10 65 79 82]

Routine, trusted indicators for fluid management, such as central venous pressure, are likely to be unreliable because of the gas trapping and pulmonary tamponade effect. Damage to the alveolar capillary membrane is likely in lung volume reduction surgery as there is much handling of the lungs. Fluid replacement is best controlled tightly within normal maintenance levels, as for lung transplantation, with predictable causes of hypotension, such as institution of positive pressure ventilation or the effect of local anaesthetic sympathetic blockade, treated cautiously with vasoconstrictors, inotropes and small infusions of colloid.[5 72]

Positive pressure ventilation

A misconception is that any one method of positive pressure ventilation is superior. Such are the pathophysiological variants that no technique is free of a proclivity to produce haemodynamic or barotraumatic complications.[26] Apart from reports of the use of self-ventilation techniques in whole or in part of a surgical procedure, all other commonly used systems have been used with success (table 2) or, it should be remembered, with failure. Essentially, it is not the technique but how and when it is applied, as any technique may be beneficial to the individual or

Table 2 Reported ventilation mode of patients with emphysema undergoing surgery

No. of cases	Type of surgery	Type of ventilation	Reference
1	Lumbar discectomy	Self-ventilation	[8]
1	Bullectomy	Self-ventilation	[28]
1	Coronary bypass graft	High frequency jet ventilation	[58]
1	Bilateral bullectomy	IPPV	[4]
1	Bilateral bullectomy	HFJV	[47]
11	Lung transplantation	IPPV	[37]
1	Bullectomy	High frequency jet ventilation	[39]
1	Lung transplantation	Modified IPPV	[65]
17	Bullectomy—giant various	IPPV	[84]
3	Various	Modified jet ventilation	[11]
1	Descending thoracic aortic aneurysm	Modified IPPV	[20]
20	Lung reduction	Modified IPPV	[41]
N/S	Volume reduction	Modified IPPV	[79]

Table 3 Stratagems for maintaining reduced mean and peak intrathoracic pressure

Use air:oxygen mix
Reduced tidal volume
  (7–8 ml kg^{-1} [79])
  Accept hypercapnia
Limit ventilator inspiration pressure (<20 cm H_2O)
Jet techniques—reduce injector size
Increase expiration phase
  I:E ratio (1:5[79])
  Prolonged interval[11]
Avoid PEEP
Revert to self ventilation asap

Any changes to patterns best conducted under direct vision of lungs, and via a period of manual ventilation

phase of the surgical procedure.[10, 79] The basic rule is to avoid application of excessive pressure at any point during a respiratory cycle; pressure is relative in these situations and an excess, by definition, differs from point to point throughout pathological lungs. Therefore, the safest starting point is to use manual inflation applied cautiously and proceed to a mechanical method with a low frequency, low inspiratory pressures (<20 cm H_2O) and expiration patterns that are without resistance (no PEEP)[7, 41, 79] and prolonged.[10] Various stratagems can be used to maintain the ventilation pattern within the confines that reduce the potential to gas trapping and dynamic hyperinflation (table 3). Jet techniques, if not used cautiously, can produce or exacerbate barotrauma,[10] and high frequency ventilation techniques are potentially dangerous because of the likelihood that high, occult PEEP is generated.[23]

With an open chest, one if not both lungs can be observed directly and the effects of ventilation assessed. It is vital that any changes in ventilation of the operated lung should be conducted under direct vision, manually, and with caution so that any pressure applied does not exacerbate damage caused by the surgical technique or predisposed by the pathology. The key therefore is flexibility and versatility, and several ventilation modes may be indicated during a case. Thus, in a recent case in a patient undergoing lung reduction via a sternotomy (case No. 6), on occasion, conventional positive pressure was applied using a pressure-limited ventilator or manual inflation applied via a Mapleson D system, and apnoeic oxygenation, in addition to self-ventilation depending on the stages of surgery. On occasion some of these systems were applied by deliberately deflating the bronchial cuff on the double-lumen tube to limit the pressure of ventilation to the other lung by allowing a large leak.[11]

Detecting dynamic hyperinflation

An understanding of dynamic hyperinflation is the result of experience of managing asthma in which it is recognized that dysfunctional airways and peribronchial cuffing create conditions for the development of an intrinsic expiratory pressure (auto PEEP or PEEP(i)), the consequences of which are air trapping.[40, 62] Preventing compounding of these patho-physiological elements[26, 73] by the processes of anaesthesia is dependent on the use of ventilatory patterns similar to those described previously.[67] Deliberate hypoventilation with permissive hypercapnia may be preventive and the treatment of choice in the established state. It is often not difficult to meet oxygen requirements as the large functional residual capacity associated with late-stage emphysema implies that frequent tidal delivery is not necessary.

Such techniques are not failsafe and it is necessary to recognize the early signs in the clinical setting[12, 54, 63] that warn of potential fatalities[43, 52, 55] (table 4). Improvement in any of the signs on disconnection of the ventilator is pathognomic[12] of a tension pneumothorax or of dynamic hyperinflation having a critical effect on cardiac function.[26] This simple manoeuvre may be life-saving until the tension is relieved with intercostal drainage or an appropriate ventilation mode established.

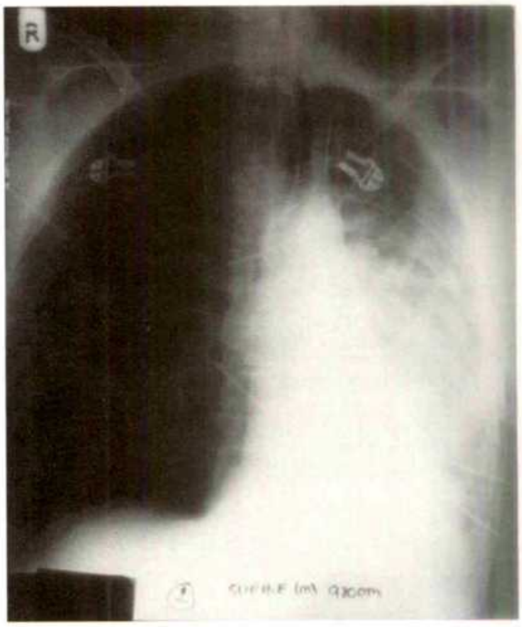

Figure 3 AP chest, case No. 8. The left lung is a transplant, compressed by the remnant native right lung.

Table 4 Detection of tension pneumothorax or dynamic hyperinflation in a clinical setting

Sign	Comment	Reference
Increased JVP	Difficult to see in patient undergoing surgery	[43]
Respiratory monitor waveform	Microprocessor controlled ventilators	[25, 30, 67]
Arterial trace waveform	Invasive arterial monitoring	[63]
Pulse oximetry	Paradoxical effect on arterial pressure and oxygenation	[11, 43]
Effect of disconnecting the ventilator	May be life-saving	

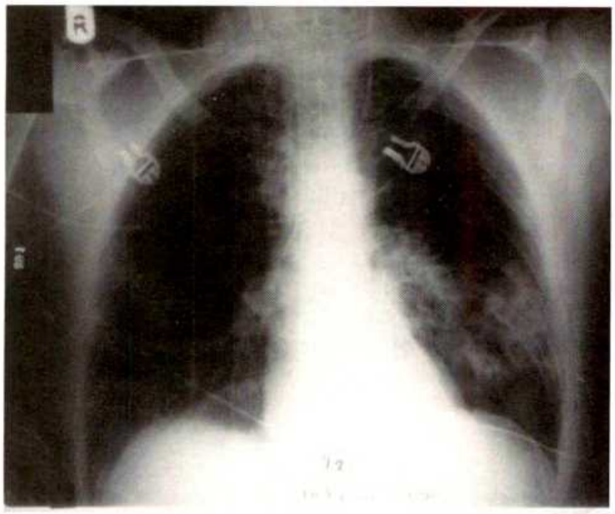

Figure 4 As in figure 3. A double-lumen tube has been placed in the right main bronchus. Independent lung ventilation has been started and the mediastinum has shifted centrally enabling the transplant to function.

Intensive care

It is possible to extubate the trachea of a patient who has undergone single lung transplantation at the end of surgery (case No. 8), and it is the norm to do so shortly after lung volume reduction surgery. However, this council of perfection cannot always be met. Single lung transplants characteristically[5 7 37] develop air trapping in the remnant natural lung which causes mediastinal shift and compromises the transplant. In the main, return to self-ventilation facilitates natural adjustments that sustain gas exchange but a few require double-lumen tube intubation and even a period of independent differential lung ventilation before this is possible (case No. 9, figs 3 and 4). For those who have already undergone extubation but are unable to maintain satisfactory blood-gas status, the use of vigorous physiotherapy, minitracheostomy and non-invasive methods of respiratory support should precede elective ventilation, which ultimately is a last resort and is associated with a poor prognosis. The use of Heimlich valves in those with small, but persistent air leaks can enable early discharge from high dependency units to the wards or even home.

Lessons for the non-specialist

As patients with a degree of emphysema are relatively common in the hospital population it is important to recognize the early signs of tension pneumothorax and dynamic hyperinflation. Knowledge of the negative effects on cardiac inotropism of air trapping exacerbated by positive pressure ventilation have been known for a long time.[32] But in the recent literature a few reports have suggested that the consequent dynamic hyperinflation is not as widely recognized as it should be by those involved in administering anaesthesia and resuscitation.[48 52] Signs may masquerade as primary right heart dysfunction or be interpreted as a pulmonary embolus of air, blood or tumour as the pulmonary tamponade acts in a similar way to a tourniquet on the heart.

Major, non-thoracic surgery is possible in those significantly compromised by bullae or emphysema.[8 20 36 58 61] Careful attention to detail, the use, whenever possible, of spontaneous ventilation and local anaesthetic techniques, and extradural analgesia during and after operation are key elements to success. The pursuit of normocapnia is a prerogative that can be sacrificed to a moderate degree ($Pa_{CO_2} \leqslant 12$ kPa).[5 9 10 53 65 82] Cannulation of a bulla, either accidental or therapeutic[44] to pre-empt the development of a tension pneumothorax,[20] may lead to the development of an air leak, requiring specialist surgical management and should not be undertaken lightly.

The efficacy of removal of functioning lung tissue in lung volume reduction surgery in improving patients in respiratory failure is a paradox that poses fundamental questions about accepted limits on lung resection and operative tolerability.[80] It is common for these patients to have pulmonary function less than 25% of predicted values. Previous constraints on surgery on grounds of fitness and arbitrary levels of respiratory dysfunction, such as carbon dioxide retention, minimal levels of forced expiratory volumes or maximum breathing capacities that equate with realistic effort required to maintain normocapnia,[11] are no longer tenable without qualification. The important distinction at a clinical level is between surgery that rapidly results in improvement in baseline (before surgery) lung function and improved chest wall dynamics, and that in which further deterioration (from baseline) is inevitable. This separates surgery for respiratory failure (lung transplantation and lung volume reduction surgery) from that for pulmonary resection for bronchogenic tumours and respiratory failure patients undergoing emergency surgery for lesions outside the thoracic cavity. In the latter there is a lag period as a result of a decrease in lung, chest wall and diaphragm compliance, attributable to the multifarious traumas of surgery, before improvement in pulmonary function. In the former, extubation can usually be performed early, while the latter probably requires positive pressure ventilation support after operation for a period until lung function returns to baseline.

Imperatives of the third age of thoracic anaesthesia

Maintenance of functional residual capacity and normocapnia are no longer the main imperatives. Important though these are, it is perhaps ironic that the greatest danger to patients is positive pressure ventilation and volume recruitment, long seen as the salvation for the management of respiratory failure. The breakthrough that has enabled anaesthesia to contribute to the reduction in mortality and morbidity of surgery for respiratory failure is prevention, recognition and treatment of barotrauma and dynamic hyperinflation.

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SHORT COMMUNICATIONS

Granisetron reduces the incidence of nausea and vomiting after middle ear surgery

Y. FUJII, H. TOYOOKA AND H. TANAKA

Summary

We studied the efficacy of granisetron, a selective 5-hydroxytryptamine type-3 receptor antagonist, in preventing postoperative nausea and vomiting (PONV) after middle ear surgery. In a randomized, double-blind, placebo-controlled study, 60 ASA I patients received placebo (saline) or granisetron 40 μg kg^{-1} i.v. immediately before induction of anaesthesia (n=30 in each group). A standard general anaesthetic technique was used. During the first 24 h after anaesthesia, the incidence of PONV in patients who had received granisetron was lower than in those who had received placebo (17% *vs* 63%; $P<0.05$). There were no clinically important adverse effects in either group. We conclude that granisetron, given before anaesthesia, reduced the incidence of PONV after middle ear surgery. (*Br. J. Anaesth.* 1997; **79**: 539–540).

Key words
Pharmacology, granisetron. Vomiting, antiemetics. Vomiting, nausea. Vomiting, nausea, surgical factors. Surgery, otolaryngological.

Honkavaara, Saarinvaara and Klemola[1] and Reinhart, Klein and Schroff [2] have demonstrated recently that the incidence of postoperative nausea and vomiting (PONV) after middle ear surgery is relatively high (62–80%) when no prophylactic antiemetic is given. Pharmacological methods to prevent PONV include antihistamines (e.g. hydroxyzine), butyrophenones (e.g. droperidol) and dopamine receptor antagonists (e.g. metoclopramide), but these drugs have undesirable side effects, such as sedation, hypotension, dry mouth, dysphoria, restlessness and extrapyramidal symptoms.[3] Ondansetron, a selective antagonist of 5-hydroxytryptamine type-3 (5-HT_3) receptors, is effective in preventing PONV with little adverse effects.[4] Another 5-HT_3 receptor antagonist, granisetron, is more potent and has longer acting activity against cisplatin-induced emesis than ondansetron.[5] We conducted a prospective, randomized, double-blind, placebo-controlled study to examine the efficacy of granisetron in preventing PONV in patients undergoing middle ear surgery.

Methods and results

After obtaining approval from our institutional Ethics Committee and informed consent, we studied 60 ASA I patients (43 females), aged 20–65 yr, undergoing middle ear surgery (tympanoplasty or mastoidectomy). Patients who had gastrointestinal diseases, who were pregnant or menstruating, or who had taken antiemetics within 24 h before surgery were excluded.

Premedication was not used. Patients were given, in a randomized, double-blind manner, a single dose of placebo (saline) or granisetron 40 μg kg^{-1} i.v., immediately before induction of anaesthesia. Anaesthesia was induced with thiopentone 5 mg kg^{-1} i.v., and vecuronium 0.2 mg kg^{-1} i.v. was used to facilitate tracheal intubation. After tracheal intubation, anaesthesia was maintained with 1.0–3.0% isoflurane (inspired concentration) and 66% nitrous oxide (which was replaced by air before closing of the tympanic membrane) in oxygen. Opioids were not given before tracheal intubation or during maintenance of anaesthesia. Ventilation was controlled mechanically and was adjusted to maintain $P\text{E}'_{CO_2}$ at 4.6–5.2 kPa throughout surgery. Neuromuscular block was produced with vecuronium and antagonized by a combination of atropine 0.02 mg kg^{-1} i.v. and neostigmine 0.04 mg kg^{-1} i.v. at the end of surgery. The trachea was extubated when the patient was awake. If two or more episodes of vomiting occurred during the first 24 h after anaesthesia, standard antiemetic therapy (e.g. metoclopramide) was given. After operation, patients received indomethacin 50 mg orally when they complained of pain.

After operation, each episode of PONV (nausea, retching and vomiting) during the first 24 h after anaesthesia was recorded by nursing staff who had no knowledge of which treatment patients had received.

YOSHITAKA FUJII*, MD, HIDENORI TOYOOKA, MD, Department of Anaesthesiology, University of Tsukuba Institute of Clinical Medicine, Tsukuba City, Ibaraki, Japan. HIROYOSHI TANAKA MD, Department of Anaesthesiology, Toride Kyodo General Hospital, Toride City, Ibaraki, Japan. Accepted for publication. May 13, 1997.

*Address for correspondence· Department of Anaesthesiology, University of Tsukuba Institute of Clinical Medicine, 2-1-1, Amakubo, Tsukuba City, Ibaraki 305, Japan.

Table 1 Patient characteristics and incidence of PONV during the first 24 h after anaesthesia. All values are mean (SD or range) or number (%). Statistical analyses were performed using ANOVA, Student's *t* test, chi-square test, and Fisher's exact probability test, as appropriate

	Placebo group (n=30)	Granisetron group (n=30)	*P*
Age (yr)	43.3 (20–62)	44.4 (23–65)	ns
Sex (M/F)	8/22	9/21	ns
Height (cm)	160.1 (8.4)	159.5 (8.0)	ns
Weight (kg)	57.2 (8.6)	56.2 (7.9)	ns
History of motion sickness (n)	3	3	ns
History of previous PONV (n)	2	2	ns
Duration of surgery (min)	213.7 (38.9)	218.2 (41.9)	ns
Duration of anaesthesia (min)	240.2 (37.9)	243.4 (44 5)	ns
Indomethacin administered after operation (n)	16	17	ns
Types of operation performed (n)			
Tympanoplasty	22	23	ns
Mastoidectomy	8	7	ns
PONV during the first 24 h after anaesthesia (n (%))	19 (63%)	5 (17%)	0.001
Nausea	10 (33%)	3 (10%)	0.029
Retching	1 (3%)	0 (0%)	ns
Vomiting	8 (27%)	2 (7%)	0.04

The treatment groups were comparable in characteristics and types of operation. During the first 24 h after anaesthesia, the incidence of PONV in patients who had received granisetron was lower than in those who had received placebo (17% *vs* 63%; P=0.001) (table 1). Six patients who had received placebo required another rescue antiemetic (e.g. metoclopramide) for treatment of two more episodes of vomiting, compared with none who had received granisetron (P<0.05). There were no adverse effects from the test drug in either group.

Comment

The aetiology of PONV after middle ear surgery (tympanoplasty or mastoidectomy) is not known precisely, but is probably associated with several factors. One of these factors is increased middle ear pressure caused by nitrous oxide.[6] Others, including age, obesity, history of motion sickness, previous postoperative emesis, surgical procedure, anaesthetic technique and postoperative pain, are also considered to increase the incidence of PONV.[3] In this study, however, no pressure was generated in the middle ear from diffusion of nitrous oxide which was replaced by air before closing of the tympanic membrane. The treatment groups were similar in characteristics, types of operation, anaesthetics administered and postoperative analgesics used. Therefore, the difference in the incidence of PONV between the groups can be attributed to differences in the drugs tested.

We found a relatively high incidence of PONV (63%) during the first 24 h after anaesthesia in patients who had received placebo. This incidence is in accordance with previous studies by Honkavaara, Saarinvaara and Klemola[1] and Reinhart, Klein and Schroff [2] who demonstrated an incidence of PONV of 62–80% in patients undergoing general anaesthesia for middle ear surgery.

It has been reported recently that granisetron is effective in the prevention of PONV after gynaecological surgery, and its safety profile is good with the recommended dose of 40 μg kg^{-1}.[7] The results of this study showed that the incidence of PONV after middle ear surgery in patients who had received granisetron was less than in those who had received placebo (P<0.05). This suggests that granisetron is effective in preventing PONV after middle ear and gynaecological surgery. The exact mechanism of granisetron in the prevention of PONV is not known, but it has been suggested that it may act on sites containing 5-HT$_3$ receptors with demonstrated antiemetic effects.[8]

This study also showed that six patients who had received placebo required another rescue antiemetic (e.g. metoclopramide) for treatment of two or more episodes of vomiting, compared with none who had received granisetron (P<0.05). Thus granisetron 40 μg kg^{-1} may reduce the severity of PONV after middle ear surgery.

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Comparison between alfentanil, pethidine and placebo in the treatment of post-anaesthetic shivering

I. J. WRENCH, G. CAVILL, J. E. H. WARD AND A. W. A. CROSSLEY

Summary

We have compared the effects of pethidine, alfentanil and placebo in the treatment of post-anaesthetic shivering. Ninety patients who shivered after routine surgery were allocated randomly to receive normal saline (n=30), alfentanil 250 μg (n=30) or pethidine 25 mg (n=30). After 10 min, 26 patients had stopped shivering in the pethidine group which was significantly more than the incidence in the two other groups (placebo=7; alfentanil=12) ($P<0.0002$). Alfentanil was not significantly different from normal saline in affecting shivering. We conclude that alfentanil 250 μg was not effective in the treatment of post-anaesthetic shivering. (*Br. J. Anaesth.* 1997; **79**: 541–542).

Key words
Complications, shivering. Analgesics opioid, alfentanil. Analgesics opioid, pethidine.

Post-anaesthetic shivering is a common problem in the recovery room, with detrimental effects including increased oxygen consumption and hypoxaemia.[1] Pethidine has been shown to be one of the most effective treatments for post-anaesthetic shivering.[2–4] Although its mechanism of action is not completely understood, a study using naloxone indicated that pethidine may act via kappa rather than mu opioid receptors. The anti-shivering action of pethidine is inhibited by high-dose naloxone which blocks mu and kappa receptors but not by low-dose naloxone which blocks only mu receptors.[3] Previous work on the efficacy of mu opioid receptor agonists in the treatment of shivering has been conflicting.[2 4] However, in an audit of postoperative shivering it appeared that intraoperative administration of the mu opioid receptor agonist alfentanil was associated with a reduced incidence of postoperative shivering.[1]

In order to investigate further the importance of mu opioid receptors in the treatment of shivering, we have compared the actions of alfentanil and pethidine. Alfentanil 250 μg was used as this is equi-analgesic to pethidine 25 mg,[5] the dose often used to treat shivering.[2] As alfentanil is a more specific mu agonist than pethidine, an equi-analgesic dose should have at least as great an effect on mu receptors. It should also follow that if pethidine acts principally via mu receptors in the treatment of shivering, this dose of alfentanil should be at least as effective.

Methods and results

The study was approved by the local hospital Ethics Committee. We studied 90 patients of both sexes, aged 18–70 yr, who developed shivering in the recovery room. All patients were ASA class I or II and had undergone routine general, orthopaedic, gynaecological or ENT surgery. As a consequence of the patients being selected as they recovered from anaesthesia, their consent was not considered valid and with agreement from the hospital Ethics Committee, informed consent was not obtained. Patients with any contraindications to the use of alfentanil or pethidine were not included.

Routine care for patients in this hospital suffering from postoperative shivering consists of oxygen 4 litre min^{-1} by Hudson mask and covering with a heat reflective blanket. In addition, each patient received an i.v. bolus dose of saline, pethidine 25 mg or alfentanil 250 μg in a total volume of 5 ml. Syringes containing the drug were prepared by recovery room staff after written instructions removed from a sealed envelope. The envelopes were inserted in a random order generated by microcomputer using a shuffling technique.

The investigator giving the i.v. injection was unaware of the treatment received by the patient and assessed the shivering grade before treatment according to a five-point scale: 0=no shivering; 1=one or more of the following: piloerection, peripheral vasoconstriction, peripheral cyanosis without other cause, but without visible muscular activity; 2=visible muscular activity confined to one muscle group; 3=visible muscular activity in more than one muscle group; and 4=gross muscular activity involving the entire body. Tympanic membrane temperature was measured (First Temp

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I. J. WRENCH, MB, CHB, BMEDSCI, PHD, FRCA, J E. H WARD, BMEDSCI, BM, BS, FRCA, Department of Anaesthesia, Royal Hallamshire Hospital, Glossop Road, Sheffield S10 2JF. G. CAVILL, BSC, MB, CHB, FRCA, A. W. A. CROSSLEY, MB, CHB, FRCA, University Department of Anaesthesia, Queen's Medical Centre, Nottingham NG7 2UH. Accepted for publication. May 6, 1997.

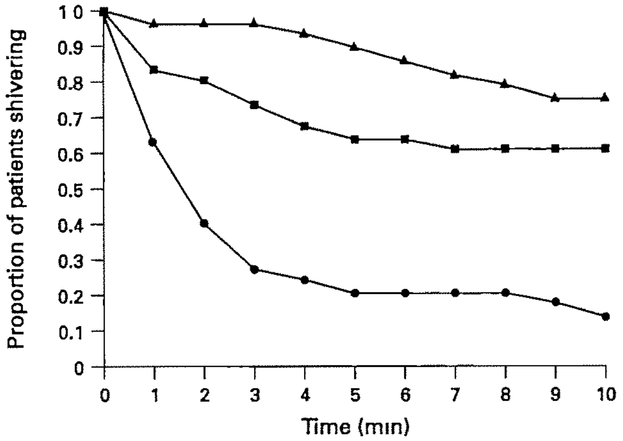

Figure 1 Proportion of patients who continued to shiver at each time in the placebo (▲), pethidine (●) and alfentanil (■) groups (n=28 for the placebo and n=30 for the two other groups). Chi-square analysis at 10 min showed that pethidine was significantly more effective than the two other groups ($P<0.0002$).

Genius Thermometer) immediately before giving the drug and shivering was assessed every minute for 10 min.

From previous work we estimated that a group size of 28 patients was sufficient to detect a 40% reduction in the incidence of shivering relative to placebo with a power of 0.85 at the 5% level.

All three groups had a median shivering grade at entry of 3 (range 2–4). Mean temperature at the time of treatment was similar in all three groups: 36.2 (SD 0.7) for placebo, 36.6 (0.8) for the pethidine group and 36.3 (0.7) for the alfentanil group. None of the patients recommenced shivering after they had stopped. Two patients in the placebo group were excluded as they received morphine for pain relief during the study.

After 10 min, four patients who had been given pethidine continued to shiver compared with 18 in the group given alfentanil and 21 in the placebo group (fig. 1). Chi-square analysis showed that pethidine was significantly more effective than both of the other treatments ($P<0.0002$). Alfentanil did not differ significantly from saline.

Comment

We have shown that alfentanil 250 μg was not significantly different from placebo in the treatment of post-anaesthetic shivering. However, fewer people shivered in the alfentanil group compared with the saline group at every time studied, indicating the possibility that a higher dose may have been more effective. This has been found to be the case with fentanyl; 25 μg (i.e. 0.36 $\mu g\ kg^{-1}$ for a 70-kg man) did not reduce post-anaesthetic shivering[2] whereas 1.7 $\mu g\ kg^{-1}$ (i.e. five-fold greater) was as efficacious as pethidine.[4] As indicated above there is evidence that pethidine may act via kappa opioid receptors in the treatment of this condition. Fentanyl also binds to kappa receptors, although five-fold more weakly than pethidine when binding to mu opioid receptors is used as a reference.[6] It is possible, therefore, that fentanyl, when given in a relatively high dose, acts via kappa receptors to stop post-anaesthetic shivering. This may also be the case for other mu agonists such as alfentanil.

In conclusion, we found that alfentanil 250 μg did not differ from placebo in the treatment of post-anaesthetic shivering. Our results are consistent with the hypothesis that kappa opioid receptors are more important than mu opioid receptors in the treatment of this condition.

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CASE REPORT

Thermal softening of tracheal tubes: an unrecognized hazard of the Bair Hugger active patient warming system

J. L. AYALA AND A. COE

Summary

The Bair Hugger system is a new and highly effective active patient warming system which produces a layer of warm air between the patient and the warming system. We report an instance of marked softening and distortion of a polyvinyl chloride tracheal tube caused by this layer. We also present laboratory data indicating that this is a likely problem under routine theatre conditions, with suggestions for prevention. (*Br. J. Anaesth.* 1997; **79**: 543–545).

Key words
Equipment, warming devices. Equipment, tubes tracheal.

Case report

A 61-yr-old man was given a general anaesthetic for left ilio-femoral arterial grafting. He weighed 67 kg and was classified as ASA III because of peripheral vascular disease limiting his exercise tolerance. After i.v. induction of anaesthesia and neuromuscular block, his trachea was intubated with an uncut polyvinyl chloride tube (Mallinckrodt Medical, "Lo-Pro" Magill, 32 cm length, internal diameter 8.0 mm). The tube was connected to a lightweight disposable ventilator system (Armstrong Medical Services Quality Disposable Systems) through a heat and moisture exchanger (HME 10, Pharma Systems AB), forming part of a circle system. The combined total weight of these connections was 275 g, measured by a Mettler PC 24 electronic balance (Mettler Instruments, Zurich). Intermittent positive pressure ventilation was commenced with the following ventilator settings: tidal volume 700 ml, ventilatory frequency 8 bpm and inspiratory flow 30 litre min^{-1}. The "Torso" attachment of the Bair Hugger active patient warming system was attached to the patient, and a model 500 E warming unit (Augustine Medical Inc.) connected and switched on at the 43 °C setting.

Thirty five minutes after surgery commenced, the tracheal tube was noted to have moved from its original vertical attitude to the position shown in figure 1. There was a marked kink in the tube at the corner of the mouth and ventilator peak inflation pressures had increased from 18 to 35 cm H_2O. As the ventilator alarm had been set too widely, responding to peak airway pressures less than 10 and greater than 60 cm H_2O, no alarms were activated. Total obstruction did not occur because of early observation of the problem. To correct the situation, the tube was cut to 22 cm, leaving nothing outside the mouth. The temperature beside the bent tube, with the warm air system working, was 40 °C, as measured using a thermocouple with internal electronic calibration (Hewlett Packard Met 530, HP 21075 A).

LABORATORY STUDY

It was clear that the dangerous tube distortion we had observed was an effect of thermal softening. As active patient warming is in daily use at our institution and as leaving polyvinyl chloride tracheal tubes uncut and self-supporting is common practice, we contacted the tube manufacturers to see if they had any data on thermal softening of their product. Their data related to normal body temperature ranges only. We performed some simple bench tests to investigate the problem.

METHODS

Figure 2 shows the test apparatus used to simulate theatre conditions. It shows a water bath with a tracheal tube anchored in the water and fixed at its other end to some ventilator system tubing and a heat and moisture exchanger. The height of this end of the tube was measured using a fixed vertical scale. A Bair Hugger patient attachment was draped over the tracheal tube and water bath. Tests were carried out in an air conditioned operating theatre with the doors closed. All temperature measurements were made using the same thermocouple thermometer with internal calibration (Hewlett Packard M1029 A). The mean response time for this probe to register stable readings over the full range of temperatures used in the tests was 135 s, measured over five cycles. Calibration of the probe was verified against a platinum resistance wire thermometer in the Process Control Calibration Laboratory at British Steel,

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J. L. AYALA, MB, CHB, DA, A. COE, MB, CHB, DA, FRCA, Department of Anaesthesia, Scunthorpe and Goole Hospitals NHS Trust, Cliff Gardens, Scunthorpe DN15 7BH. Accepted for publication: May 8, 1997.

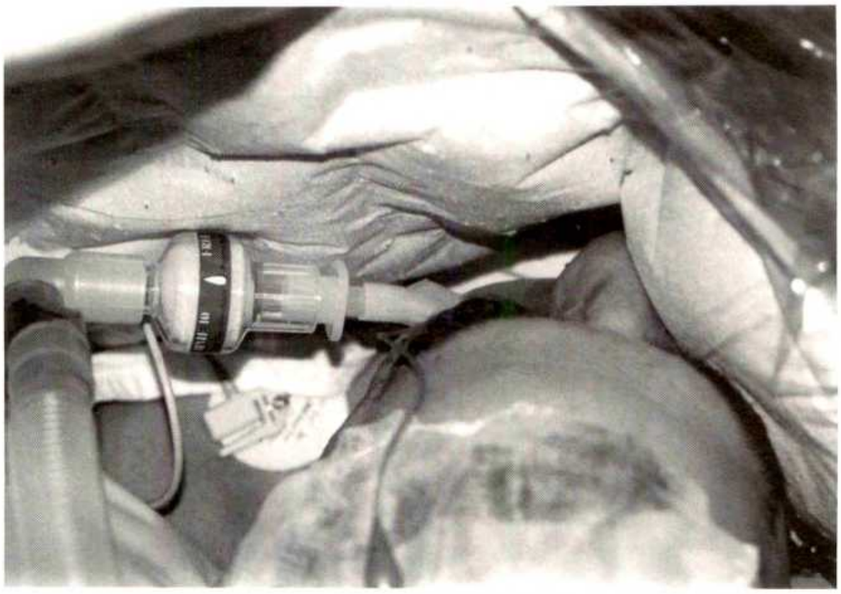

Figure 1 Photograph showing the softened polyvinyl chloride tracheal tube attached to the lightweight disposable system tubing. The tube is displaced 90° from an originally vertical position because of thermal softening.

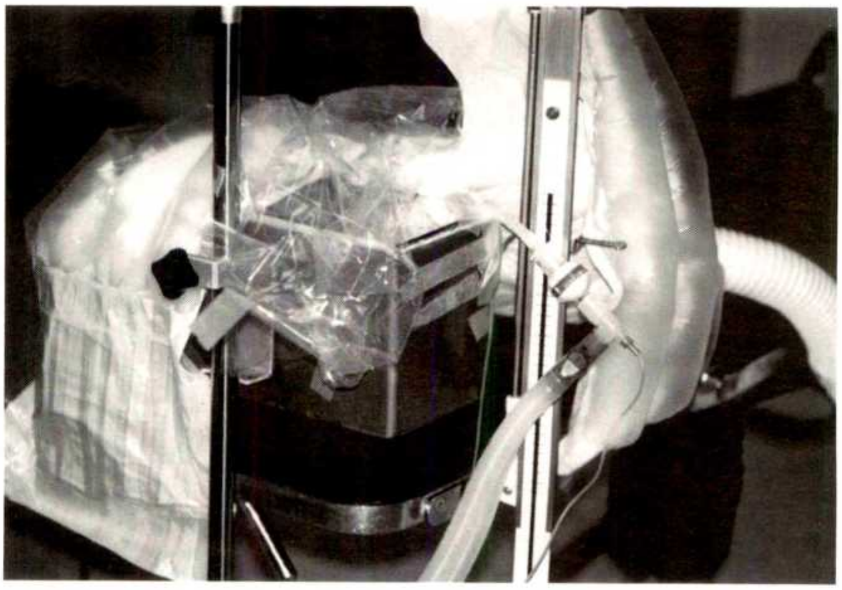

Figure 2 Thermal softening test apparatus rig showing the heated water bath, tracheal tube with displacement scale, and Bair Hugger patient warming attachment.

Scunthorpe. This instrument is checked regularly by the National Measurement Accreditation Service. Air temperature measurements were made by exposing the probe in the room, 100 cm from the apparatus. Water bath temperature measurements were made by suspending the probe in the water bath, at least 5 cm clear of the heating element.

The temperature at the tracheal tube was measured by fixing the probe 1–2 cm from the tracheal tube connector, beneath the heating blanket. The probe was not fixed to the tube itself. Missing temperature measurements in the data tables were caused by delays in obtaining stable, equilibrated temperature readings from the probe.

The water bath represents the patient in this simulation. It was kept as close to body temperature as possible during each test. Each tracheal tube was anchored to the bottom of the bath by passing its distal end through a heavy lithotomy pole bracket and to the side of the bath by adhesive tape. The same system and humidifier described in the case report were attached to the end of each tube. The humidifier was dried between tests. Measurements of deformation were made by noting the starting position on a vertical scale of the lowest point of the tube connector and measuring it again at the end of the test (fig. 2). It was thought that the arc described by this point would be very similar in length to the vertical distance measured, as the radius of the circle of motion was large in relation to the measured

Table 1 Measurements made, with timings

Time	Room temp.	Temperature at tube	Water bath temperature	Tube deformation
0 min	–	+	+	+
15 min	+	+	–	–
30 min	–	+	+	+

Table 2 Results of laboratory testing where for 50% of the tubes the warming unit remained switched off (group C) and in the other 50% it was set at its maximum setting (group H). All temperature readings are in °C

Tube No	Room temp. 15 min	Water bath temp		Temp. at tube			Tube deformation (mm)	
		0 min	30 min	0 min	15 min	30 min	0 min	30 min
Group C (controls)								
1	22.2	37.1	36.5	22.0	22.1	22.0	0	10
2	22.3	37.7	35.9	24.3	25.3	23.0	0	15
3	21.6	37.1	35.9	27.3	25.3	23.0	0	3
4	22.0	37.5	36.9	23.4	23.5	23.8	0	8
5	22.0	37.0	36.3	24.0	21.5	23.0	0	10
6	24.0	36.7	36.0	25.8	25.6	25.7	0	4
7	23.1	37.5	36.2	27.1	25.8	25.7	0	6
8	22.9	36.8	35.6	27.4		22.9	0	4
9	21.3	35.8	34.8	24.2		24.2	0	8
10	21.3	35.9	34.3	22.0	23.2	22.4	0	7
Group H (test)								
1	22.3	36.4	37.6	38.9	39.3	39.5	0	25
2	22.2	37.5	36.4	30.0	36.6	36.8	0	24
3	21.0	37.3	36.9	31.3	34.2	36.8	0	14
4	22.3	36.6	36.3	36.1	37.0	36.5	0	13
5	22.8	37.2	36.5	37.2	38.1	38.1	0	18
6	23.0	36.9	35.7	35.2	35.1	34.9	0	13
7	24.0	37.5	36.7	31.4	35.8	35.7	0	23
8	21.3	36.8	35.5	27.1	34.1	34.3	0	37
9	21.3	37.5	36.0	29.0	34.5	34.5	0	15
10	21.4	36.0	35.9	26.9	34.5	34.5	0	28

movement. During all measurements, a "Torso" Bair Hugger attachment was draped over the water bath and the tracheal tube under test. This was connected to a Model 500E warming unit. For 50% of the tubes from each batch, the warming unit remained switched off (group C). For the other 50% it was turned on at the maximum setting at the start of the test and left on for the duration of the test (group H).

Twenty tracheal tubes were tested. They were 8.0-mm internal diameter "Lo-Pro" tracheal tubes manufactured by Mallinckrodt Medical, catalogue number 102.80 (as was the tube described in the case report). The batch number of the first 10 sample tubes were 12.94 4692 and of the other 10, 02.95 5654. Five tubes from each batch were used in each test group. For each tube, measurements of temperature adjacent to the tube under the Bair Hugger attachment were made at zero, 15 and 30 min from the start of the test. Measurements of water bath temperature and tube deformation were made at 15 and 30 min into the test, and room temperature was measured at 15 min (table 1).

RESULTS

The Student's *t* test was used to analyse the data. Table 2 shows the results. There were no significant differences between the water bath temperatures and room temperatures recorded in the two groups. Mean tracheal tube deformation was significantly greater ($P<0.001$) in group C (7.5 mm) than in group H (21 mm). The tubes in group H were deformed to a greater extent.

Discussion

Active patient warming using a forced-air mattress system is a widely used and well documented technique for routine theatre purposes.[1–3] The system is relatively new and research has focused largely on comparison with existing or alternative warming techniques.[1 4] Apart from routine manufacturer's warnings, we were unable to find any published data on potential hazards.

In this case report, we noted marked thermal softening of a polyvinyl chloride tracheal tube caused by exposure to the warm air layer produced by a Bair Hugger active patient warming system. Our laboratory data indicated that this is a likely occurrence under routine theatre conditions.

In summary, tracheal tubes were warmed markedly when a Bair Hugger warming apparatus was used. The tracheal tube softening that this produced presents a threat of obstruction to the tube. The use of uncut PVC tubes is not recommended when this warming system is used. If uncut tubes are used, they must be supported adequately. High and low thresholds of pressure sensitive ventilator alarms must be set close to peak inflation pressure to give immediate warning of any obstruction.

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British Journal of Anaesthesia 1997; **79**: 546–548

CORRESPONDENCE

Low-dose dopamine: there is a scientific rationale

Sir,—Regarding the recent editorial "Low-dose dopamine: will there ever be a scientific rationale?",[1] I do not question its content, but rather what should have been included.

It is expressed clearly and well justified that low-dose dopamine probably does not save lives in intensive care units. The authors briefly mention that dopamine "...limits adenosine triphosphate utilization and oxygen requirements in nephron segments, at least for ischaemic injury....". This point is important for the justification of the use of dopamine in the protection of the kidney during a relatively short-lasting (hours) or severe ischaemic insult. This idea is derived from some anatomical and physiological characteristics of the medulla. Within the medulla, oxygen diffuses from arterial to venous vasa recta which predisposes the outer medulla to a degree of oxygen deprivation. In this region the medullary thick ascending limb of Henle's loop (mTAL) is responsible for the creation of an osmotic gradient by reabsorption of sodium. This process demands and consumes a significant amount of energy and oxygen. The rate of reabsorption at the level of mTAL is the main determinant of renal oxygen demand, and suppression of reabsorption is associated with a significant increase in medullary oxygen tension.[2] A well documented, dopamine-induced anti-aldosterone effect[3] and inhibition of Na^+–K^+-ATPase results in a decrease in solute reabsorption[4 5] and subsequently a decrease in oxygen demand in the tubules, particularly in the mTAL, the most vulnerable part of the nephron to ischaemic insult.[6–8] In addition, dopamine increases the formation and release of prostaglandin E_2[9] which dilates medullary vessels[10] and also inhibits oxygen consumption in tubular cells.[11] An increase in renal blood flow resulting from activation of DA-1 receptors might improve renal function (renal blood flow, glomerular filtration rate (GFR), sodium and water excretion) in patients with acute renal insufficiency,[12 13] however, the increase in GFR *per se*, which represents an "improvement in renal function", might be detrimental for the viability of the kidney undergoing a short but severe ischaemic insult (e.g. suprarenal aortic cross-clamping). An increase in renal cortical blood flow and GFR would be associated with an increase in transport of the solute to the tubules, an increase in reabsorption and oxygen demand.

This scientific rationale for the use of dopamine (in conjunction with other drugs decreasing reabsorption) has not enjoyed overwhelming confirmation by clinical data. There are probably many reasons for this. One may be that there is a narrow window of opportunity where any therapeutic intervention can be proved by outcome studies. In other words, the majority of patients would not need any treatment and their renal function would be preserved after a relatively short ischaemic insult; or, for some patients, the ischaemic insult would be so severe that none of the treatments could be effective. The situation can be aggravated by the different baseline status of renal function and reserves. One study of the prophylactic use of dopamine demonstrated a significant decrease in the incidence of renal insufficiency in patients undergoing angiography with impaired baseline renal function, while there was a difference in patients with relatively normal renal function.[14] Thus despite the lack of clinical data, present scientific literature seems to justify the rationale that low-dose dopamine in addition to (or in conjunction with) some other loop diuretics might protect the kidneys during ischaemic insult.

S. Gelman
Department of Anesthesia
Brigham and Women's Hospital
Boston, MA, USA

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External cooling in critically ill febrile ICU patients

Sir,—The findings of Poblete and colleagues[1] indicate that external cooling is more effective than antipyretic agents in the treatment of febrile ICU patients. As the authors noted, application of ice sponges is relatively inconvenient and the method of external cooling used in the first instance by many ICU is the rotary fan. However, an extensive literature search has revealed no studies on the efficacy of this method in these circumstances. In addition, increased risk of airborne infection is a potential concern. Fans are unlikely to act as a source of infection in the way that contaminated air conditioning systems can[2 3] but they might enhance transmission of airborne pathogens between adjacent patients. Environmental contamination of the ICU with pathogenic bacteria is well known[4] and in one ICU inadvertent circulation of air from an isolation room back into the main unit led to an outbreak of methicillin-resistant *Staphylococcus aureus*.[5] Given the ineffectiveness of antipyretic drugs demonstrated by Poblete and colleagues, further studies on the efficacy and risks of other antipyrexial therapies used in the ICU seem warranted.

A. P. Morley
Department of Anaesthesia and Intensive Care
Chinese University of Hong Kong,
Hong Kong

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Inhaled nitric oxide

Sir,—The Intensive Care Society recently published recommended safety precautions for the therapeutic use of inhaled nitric oxide (Winter 1996 newsletter). Included in these was a suggestion that when high concentrations of nitric oxide are used in areas of limited ventilation, a scavenging system should be used. A footnote added that activated charcoal absorbers were ineffective scavengers of nitric oxide. This information seems to have come from an article by Squire, Kightley and Petros[1] where the authors stated "using activated charcoal...no reduction in exhaust gas concentration was detected at any time".

We recently had reason to test if "Aldasorber" (Shirley Aldred and Co. Ltd, Bradwell, UK) activated charcoal scavenging units absorb nitric oxide. A nitric oxide mixture containing 40 ppm of nitric oxide was passed through an Aldasorber unit at 10 litre min^{-1}, and the effluent nitric oxide concentration was recorded with a chemiluminescence analyser linked to a personal computer recording at 6-s intervals. The analyser has a limit of detection of 0.05 ppm and a display resolution of 0.1 ppm in the range used. When the carrier gas was nitrogen alone, nitric oxide appeared at the outlet of the absorber almost immediately, and reached a maximum of approximately one-third of the inlet concentration (fig. 1). When the carrier gas was air, nitric oxide was detected in the effluent gas only after 13.2 h, and at 24 h the effluent concentration was only 0.1 ppm. When 40 ppm of nitrogen dioxide in nitrogen were passed at 10 litre min^{-1} through an absorber, no nitrogen dioxide was detected in the effluent gas over the 1-h period of the experiment.

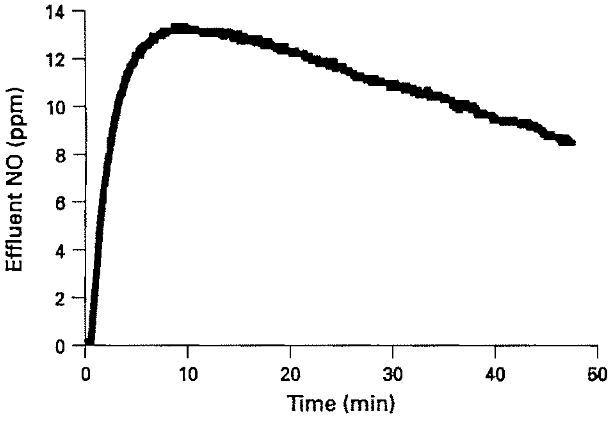

Figure 1 Effluent nitric oxide (NO) concentration when an NO mixture containing NO 40 ppm was passed through an Aldasorber activated charcoal scavenging unit.

The discrepancy between these results and those of Squire, Kightley and Petros[1] is difficult to explain. They used Carbomix (Penn Pharmaceuticals Ltd, Gwent, UK) as an absorber, a charcoal designed to be mixed into a slurry and instilled into the stomach to absorb drugs in the aqueous phase. This formulation is approximately 80% charcoal; the remainder is citric acid, acacia gum and glycerine. This presumably alters the gas absorbing properties of the charcoal. Aldasorber units are designed to remove organic anaesthetic agents in the gas phase.

Our results suggest that nitric oxide is scavenged by activated charcoal, but only in the presence of oxygen. As nitrogen dioxide is scavenged even without oxygen, it is possible that the charcoal catalyses the oxidation of nitric oxide to nitrogen dioxide which is then absorbed. Whatever the mechanism, activated charcoal would appear to be an effective scavenger of nitric oxide at concentrations used in clinical practice.

J. D. Young
Nuffield Department of Anaesthetics
Radcliffe Infirmary
Oxford
A. Rhodes
F J. Lamb
Department of Intensive Care
St George's Hospital
London

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Predominant involvement of motor fibres in patients with critical illness polyneuropathy

Sir,—Hund and colleagues demonstrated that critically ill patients may suffer from an acute axonal motor polyneuropathy which is related to sepsis, and not to the use of neuromuscular blocking agents.[1] This result has important nosological implications because the reduction in compound motor action potential (CMAP) with preserved sensory action potential has until now been taken as evidence in favour of neuromuscular blocking agent-related neuropathy (or myopathy) and against critical illness polyneuropathy (CIP).[2] However, three aspects of this study need clarification.

First, seven of 20 patients with grade 2–3 denervations were found to have CIP and normal CMAP amplitude (fig. 1[1]). This was a strange result. In axonal neuropathy the total number of nerve fibres is reduced, while myelination of surviving fibres is maintained. Therefore, CMAP amplitude (which is the sum of the action potentials of all nerve fibres) decreases while nerve conduction velocity remains normal or nearly normal. CMAP, an energy-requiring event, may be reduced at an early stage of sepsis and critical illness. In contrast, signs of denervation take several days or weeks to become evident.[2] Therefore, it would be theoretically justifiable to have reduced CMAP without signs of denervation, but the opposite situation would not be possible. In the discussion the authors stated that "these 20 patients had abnormal CMAP".

Second, it was suggested that mild CIP is unlikely to cause weaning failure. However, mild CIP of the limbs does not necessarily imply mild CIP of the diaphragm and respiratory muscles, and it would be worrying for intensive care physicians to assume that neuromuscular problems are not ongoing without carefully assessing respiratory muscles and nerves.[3]

Finally, the authors stated that myopathy was an unlikely diagnosis in their patients because creatine kinase concentration (CK) was mostly normal and asthma was not a cause of admission. Diagnosis of myopathy in critically ill unconscious patients requires muscle biopsy for confirmation. CK may remain normal but the muscle may be electrically inexcitable.[4] An electrophysiological study is not conclusive in itself. In fact, CMAP may be reduced because of motor neuropathy, myopathy or both. Furthermore, denervation signs may be seen also in myopathy when the necrotic process disconnects the end-plate zone from the active membrane.[5] We have shown that many septic patients with an electrophysiological diagnosis of CIP had a myopathy at biopsy.[6]

Sepsis does not spare muscle and critical illness myopathy is at least as frequent as CIP,[6] provided the correct investigations are used. If biopsy is not planned, diagnosis of neuromuscular disorder would be more appropriate.

N. Latronico
A. Candiani
Istituto di Anestesia e Rianimazione
Spedali Civili
University of Brescia
Brescia, Italy

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Sir,—Thank you for the opportunity to respond to the comments of Drs Latronico and Candiani. As in other studies, CIP was defined in our study as newly occurring pathological spontaneous activity in resting muscles during ICU treatment.[1 2] Although CMAP amplitudes are usually reduced, we encountered patients who had normal CMAP amplitudes despite severe denervation activity on EMG. For example, in patient No. 14, who had severe sepsis after major abdominal surgery, median nerve CMAP amplitude was 8.1 mV and SNAP 22 µV at the time of grade 3 denervation activity in all muscles examined. Patient No. 17, with polytrauma and severe head injury, had a median nerve CMAP of 6.0 mV and SNAP of 84.9 µV (*sic*) shortly before death. In this patient, grade 3 denervation was present for 2.5 weeks. The reason for this finding is unclear. So far the exact mechanism and type of lesion in CIP has not been elucidated. Thus when confronted with CIP, one should bear in mind that classical polyneuropathy, characterized by dying-back type axonal degeneration, is most likely not involved. Evidence for other mechanisms comes from electrophysiological studies and the observation that recovery is often very fast, that is much faster than expected in chronic axonal degeneration.[3]

Among the many authors reporting on CIP, only Bolton advocates phrenic nerve conduction studies and electromyography of the diaphragm.[1] Until now, his group has published one series in which such studies were included.[4] In this series, four of 16 patients with bilateral phrenic neuropathy had mild CIP according to electrodiagnostic examination of the limbs. One of these patients also had abnormal central respiratory drive. The degree of phrenic nerve involvement and diaphragmatic denervation was not quantified. Although we cannot exclude the possibility that some of our patients had significant phrenic neuropathy despite only minor abnormalities of the limbs, we feel that this is quite unusual in a generalized disorder such as CIP. We agree, however, that diaphragmatic EMG and phrenic nerve conduction studies should be performed in patients with persistent failure to wean, if repeated limb electrodiagnosis shows only minor abnormalities.

We discussed the issue of myopathy in our article. Most authors diagnose patients as having CIP without performing muscle biopsy. In general, such florid denervation activity, as observed in patients with CIP, is unusual in myopathy. After the advent of the report of Rich and colleagues,[5] we included testing of electrical excitability of muscles in our protocol. So far none of our patients has been found to have electrically inexcitable muscles (unpublished result). Latronico and colleagues had a high number of patients with myopathic features on histopathological examination who were diagnosed as having only CIP on the basis of electrodiagnosis.[6] However, all but two patients biopsied late in the disease course had histopathological findings consistent with the electrophysiological results. Thus in the later stages of sepsis, electrodiagnosis alone may give reliable results, while in the early disease state, muscle biopsy may be necessary for a correct diagnosis.

E. HUND
Department of Neurology
Ruprecht-Karls-University
Heidelberg, Germany

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British Journal of Anaesthesia 1997; 79: 549

BOOK REVIEWS

Applied Cardiovascular Physiology. (Update in Intensive Care and Emergency Medicine Series). M. R. PINSKY (editor). Published by Springer, Berlin. Pp 263; indexed: illustrated.

This is a slim volume in the series from Springer, *Update in Intensive Care and Emergency Medicine.* It is a multi-author text and is aimed at those providing acute medical care.

The book is divided into four sections: basic cardiovascular physiology, clinical applications, goals of resuscitation and cardiovascular support by haemodynamic subset.

The first section, on cardiovascular physiology, is the longest in the book and provides good coverage of both established concepts in cardiovascular physiology and some newer ideas. The chapter on left ventricular function gives an excellent readable account of left ventricular haemodynamics. That on AV coupling is a useful introduction to the application of engineering concepts to this problem in haemodynamics. The discussion of the cardiovascular management of the critically ill patient is excellent and provides a valuable account of the mechanism and impact of various cardiovascular manipulations. I found the account of the effect of stressed and unstressed volume on venous return particularly useful.

The second section, clinical applications, deals with issues in haemodynamic monitoring. Many of the concepts on invasive haemodynamic monitoring are already known to many readers but this chapter contains useful material. The distinction between wedge pressure and pulmonary artery occlusion pressure is well made. There is a good considered review of the value of trans-oesophageal echocardiography which many readers will find of value as this technique becomes more widespread. One criticism of this section is that the discussion of the rationale for haemodynamic monitoring tends to avoid the vexed issue of the lack of studies which show an impact of haemodynamic monitoring on outcome and chooses to emphasize the perhaps self-evident fact that such monitoring allows cardiovascular manipulations to be undertaken.

The third section, goals of resuscitation, introduces the relationship between Do_2 and Vo_2, which is a major theme in the remainder of the book. The nature of the relationship and its physiological and pathophysiological basis are dealt with at length. The current uncertainty regarding supranormal haemodynamic targets is well discussed.

The final section on cardiovascular support by haemodynamic subset aims to focus attention on important aspects of cardiovascular support in various types of cardiovascular failure. The chapter on cardiogenic shock is excellent. That on septic shock is to some extent a catalogue of the effects of different cardiovascular drugs and I found it heavy going. The final chapter on extracorporeal support was somewhat lacking in detail. There was a conspicuous absence of any discussion of the lack of randomized controlled studies showing benefit from extracorporeal techniques in adults.

I have two criticisms of this book, both minor. The book focuses on the impact of physiological interventions on the cardiovascular system rather than on outcome. However, there is some discussion of the effect of interventions on outcome and this is primarily a physiology text. More importantly the book would have benefited from more rigorous editing and proof reading. In some chapters the use of English is strained and there are significant numbers of duplicated words and other grammatical errors.

On balance, this is an useful book. It is not a text for the examination candidate but will be of interest to the established practitioner. It is slim enough to be read from cover to cover. The specialist in intensive care or cardiovascular anaesthesia will find much which is valuable and the generalist will certainly find information of interest.

S. J. Howell

Principles and Practice of Pharmacology for Anaesthetists, 3rd Edn. T. N. CALVEY AND N. E. WILLIAMS. Published by Blackwell Science, Oxford. Pp. 596; indexed; illustrated. Price £75.00

This is the third edition of a book which has long been popular with candidates preparing for FRCA examinations. In the 6 yr since the second edition was produced there have been several new drugs introduced and advances in the theories of drug action The authors have revised and updated all of the chapters although the overall format remains the same.

The book contains 17 chapters, each 30–40 pages long The book can be divided into three, roughly equal sections. The first section has six chapters on general pharmacology which covers drug uptake and elimination, pharmacokinetics, drug action, isomerism, drug interactions and variability in drug response. The second section covers anaesthetic drugs and in five chapters deals with i.v. anaesthetics, inhalation agents, local anaesthetic agents, drugs acting on the neuromuscular junction and analgesic drugs. The final section deals with drugs acting on other systems and includes six chapters on the autonomic nervous system, premedication and antiemetics, antihypertensives, anti-arrhythmic and anti-anginal drugs, anticoagulants and corticosteroids, and hypoglycaemics. There are no specific chapters on the respiratory, gastrointestinal or renal systems. However, the majority of these drugs are covered within some of the aforementioned chapters. For example, asthmatic drugs are covered in the autonomic nervous system and diuretics under antihypertensive drugs (although one would not usually expect to find mannitol under such a heading).

Individual chapters are clearly divided into appropriate sections. At a glance the text for each drug would appear to be short but on reading it it is clear that it is packed with facts. Hence while the text is not that of a comprehensive reference textbook it is appropriate for those studying for examinations. There are relatively few figures but those that are included are clear and comprehensive, and link well with the text. The text is not referenced but each chapter provides a list of about 50–60 articles for further reading. The majority of these are from the 1980s, perhaps reflecting the age of most of the drugs described, but references up to 1996 are included. Overall, I think this book will justifiably remain popular with candidates preparing for FRCA examinations and will also be a useful quick reference book for practising clinicians.

C. S. Reilly

Papers for publication and all editorial communications should be addressed to:
Dr J. M. Hunter,
Editor-in-Chief, *British Journal of Anaesthesia,*
University Department of Anaesthesia,
Royal Liverpool University Hospital,
The Duncan Building,
Daulby Street,
Liverpool L69 3GA.
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"I would have everie man write what he knowes and no more."—MONTAIGNE

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EDITORIAL I

"Walking extradurals" in labour: a step forward?

The ideal analgesic drug or technique for use in labour should be simple and safe to administer with no adverse short- or long-term effect on the mother, no effect on progress of labour and have either a beneficial effect or no effect on the fetus. Most importantly, it should decrease or abolish the pain of labour without affecting other sensations such as the desire to push. Such an analgesic or analgesic method does not exist. Until recently, extradural administration of local anaesthetic solutions have been used to abolish the pain of labour but a proportion of women find the motor block produced by such solutions unacceptable.[1] In addition it has been suggested that extradurals are associated with long-term back pain,[2 3] and increased Caesarean -section[4] and instrumental delivery[5] rates. However, all of these associations have been vociferously challenged.[6–9]

Complete motor block is not an inevitable consequence of extradural analgesia.[10] Several techniques have been used to reduce or even abolish this in an attempt to produce selective nociceptive block. In evaluating such techniques it should be established if the objective of treatment is to allow movement in bed or normal walking. Walking in labour, considered here, with good extradural pain relief, is possible and is associated with a greater degree of maternal satisfaction than non-mobile techniques.[11] The fact that demand for extradurals has increased dramatically in hospitals where ambulatory extradurals have been introduced has implications for anaesthetic workload and staffing.[1]

The adoption of the recumbent position (wedged supine) throughout labour facilitates monitoring of the mother and fetus. However, it may also have adverse effects on duration of labour, requirements for analgesia, fetal heart rate abnormalities and the chance of operative delivery, although this is controversial.[12] Some authors have strongly criticized the treatment of women in labour as ill patients[13] and the adoption of the recumbent position in a hospital bed may contribute to this attitude. Relatively few studies have specifically encouraged walking, but if this is the objective of treatment then it may involve additional risks while providing benefits other than preserving motor power.

Cardiotocograph (CTG) monitoring of the fetus in women who are mobile is difficult but telemetric CTG devices are available commercially. In some centres the CTG is only intermittently monitored routinely in walking women receiving extradural analgesia with no apparent adverse effect.[14] However, other authors have described CTG abnormalities after intrathecal administration of sufentanil to women in labour and recommend the use of continuous monitoring for 1 h after administration.[15]

The requirements of safe walking with regional block are muscle power, proprioception and a subjective feeling of ability to walk,[1] in addition to vision and an intact vestibular apparatus.[16] Surprisingly, many authors have allowed mobilization based solely by testing power against resistance while recumbent, such as straight leg raising,[11] the Medical Research Council (MRC) score[17] and Bromage[18] score. After one of their patients fell with no detectable weakness on the Bromage scoring system, Breen and colleagues[19] modified the assessment to include a partial knee bend. This may be a more appropriate assessment because it tests dynamic power of the hips, knees and ankles which are involved in lifting the subject's own weight. Buggy, Hughes and Gardiner[20] concluded that patients who had apparently normal power (assessed by MRC score), some of whom felt able to walk, should not be allowed to do so because of significant posterior column sensory impairment resulting in proprioceptive loss. Others have noted that proprioception is not necessary for walking, providing that vision and motor power are preserved,[16] and that the doses of extradural drugs used by Buggy, Hughes and Gardiner[20] were significantly greater than those used by other authors who advocated walking.[21] Posterior column function has been assessed subsequently in more appropriate "walking extradurals" and found to be preserved.[22 23] It is unclear what tests are required. A modified Bromage score of 6 (partial knee bend while standing),[6] a test of proprioception such as Romberg's sign and a supervised trial walk would seem to be the minimum test requirements. In any event, women should be supervised at all times and their walking supported with an appropriate adult in case of unsteadiness.[10]

The effects of supine hypotension caused by aortacaval compression on the mother and fetus are well known and the extremes of lateral tilt required to abolish it have been described previously.[24] It is possible that the upright position further attenuates aortacaval compression, reducing the effects of venous pooling on maternal arterial pressure and fetal heart rate in the standing position.[25] The effect of analgesia in walking mothers on mode of delivery is unclear but there is some evidence that reducing motor block and encouraging walking is associated with a decreased rate of instrumental[26,27] and operative delivery.[28] In other studies this difference was not statistically significant.[29] A pilot study showed a non-significant increase in normal delivery rates in women who had received "walking extradural" analgesia who were allocated randomly to stand or stay supine 1 h before pushing in the second stage of labour.[30]

Studies that have been designed to encourage walking usually rely on institution of analgesia with a mixture of low-dose local anaesthetic and opioid administered into the extradural or subarachnoid space followed by a further mixture given into the extradural space. A well described technique in the UK is a combined spinal–extradural (CSE) technique using a subarachnoid dose of 2.5 mg of plain bupivacaine and 25 μg of fentanyl, followed by extradural boluses of 10–15 ml of bupivacaine 0.5–1 mg ml^{-1} and fentanyl 2 μg ml^{-1}.[14] Other opioids such as sufentanil[29] (not available in the UK) and alfentanil[31] have also been used. Studies are awaited using ropivacaine and L-bupivacaine which may further reduce motor block associated with extradural analgesia. Other studies have included administration of α_2 agonists such as clonidine or adrenaline, in some cases without the use of local anaesthetic,[32] although the role of these agents in labour is unclear.

The main advantages of initial subarachnoid administration of an anaesthetic mixture are speed of onset of analgesia (usually within 5 min of administration)[11,33] and increased maternal satisfaction. It has been suggested that this initial dose reduces subsequent requirements for analgesia and therefore preserves the ability to walk in late labour.[1] Possible disadvantages are a relatively high incidence of failure to puncture the dura with the spinal needle[1]; this occurs in approximately 5–10% of cases using the "needle through needle" CSE technique, despite correct placement of the Tuohy needle in the extradural space.[1,11,14,34] It is possible that routine dural puncture with the spinal component of CSE may produce an increased incidence of post-dural puncture headache (PDPH)[34] but the pencil-point needles used are associated with a relatively low rate of headache.[35] An initial high rate of PDPH reported by workers at Queen Charlotte's Hospital was not evident in subsequent studies.[1,11,14] In a study where the incidence of dural puncture was extremely high, puncture with the Tuohy needle occurred less often during CSE than with extradural insertion alone (1.7% *vs* 4.2%).[34]

Another problem reported with CSE is subsequent insertion of the extradural catheter into the CSF after dural puncture with the spinal needle.[36] A cadaveric study using Quincke-tipped needles showed that this was virtually impossible.[37] Such cases are more likely to have occurred through inadvertent dural puncture with the Tuohy needle and therefore the risk of subarachnoid catheter insertion is the same whether CSE or extradural alone is used. The first use of any extradural catheter must be under the direct supervision of personnel able to manage the consequences of inadvertent subarachnoid administration, particularly where an extradural catheter "test dose" has not been given.

Cases of meningitis have been reported after CSE.[38] Apparent risk factors include chemical contamination of equipment with sterilizing fluid and multiple extradural and dural punctures. The many causes of aseptic and septic meningitis after central blocks have been reviewed recently in an editorial which may reassure proponents of CSE.[39] However, even a relatively low excess incidence of associated meningitis in routine clinical practice would make any new technique unacceptable.[40]

The subarachnoid component of CSE provides analgesia superior to an extradural alone particularly when used in late labour and may preserve the ability to walk in late labour. However, the disadvantages, which are not insignificant, have caused several authors to question the routine use of dural puncture to facilitate analgesia in labour[40,41] and this is the subject of several studies in progress.

Maintenance of extradural analgesia may be provided by continuous infusion, patient-controlled extradural analgesia (PCEA) or traditional boluses. A significant advantage of mechanical administration of extradural mixtures by infusion or PCEA is that in many centres in the UK midwives are not allowed to administer boluses of mixtures of drugs[42,43] into the extradural space. Infusions are associated with a greater incidence of motor block in late labour because administration of local anaesthetic may be greater than a patient's requirements.[44] If mobility is important in late labour[30] then gradually increasing motor block would be a disadvantage with infusion-based techniques. A criticism of PCEA in walking women is the possibility of receiving a self-administered bolus of extradural solution in the absence of a midwife.[41] The use of extradural infusions but not PCEA has been associated with a greater need for medical assessment and administration of analgesia.[43,45,46] Some authors have found PCEA pumps unreliable in a walking population.[47] Significant advantages of PCEA are increased maternal satisfaction, feelings of self-control and a dose-sparing effect compared with continuous extradural infusion.[43,46]

Many hospitals in the UK have provided extradural services for decades with conventional extradurals. The fact that their side effects are so controversial, and serious side effects such as death or major neurological sequelae are so rare provides evidence for the inherent safety of the technique. It is possible that "walking extradurals" are associated with side effects which may preclude their use in labour. If any new technique is to be introduced it needs to be evaluated carefully first to establish any superiority and second to monitor side effects. In their first series of patients, workers at Queen Charlotte's Hospital found an initial high incidence of side effects such as PDPH and these diminished with time.[1,11,14] This would indicate that such techniques are not for occasional use by inexperienced personnel.

Mobile extradural techniques have the potential to provide pain free, enjoyable labour with possibly more chance of normal delivery and fewer long-term side effects than conventional extradurals. The case for the widespread use of such techniques has not yet been made. Further work is necessary to establish the benefits of such procedures and to justify the routine use of dural puncture in all women requesting central block in labour rather than extradural administration alone. To date the only convincing evidence is that CSE is associated with increased maternal satisfaction and earlier onset of analgesia.

C. D. Elton
P. Ali
M. C. Mushambi
Department of Anaesthesia
Leicester Royal Infirmary
Leicester LE1 5WW

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EDITORIAL II

Anaesthesia and the competence revolution

An assessment is what we do when we wish to measure the outcome of an episode of learning. It may take many forms such as an examination, a multiple-choice questionnaire (MCQ), an oral examination, an objectively structured clinical examination (OSCE) or a workplace observation. Every assessment should conform to a simple set of rules: it must have a purpose, an outcome, validity and reliability. A valid assessment is one that measures what it is supposed to measure. A reliable test is one that produces the same results if the candidate immediately retakes the test and irrespective of which examiner marks it. An assessment also expresses something about the philosophy of education and learning. Traditional academic education is associated with the view that learning trained the mind in ways that were of general benefit to future performance. This view of "liberal education" was expressed by Cardinal Newman (1852)[1]: "Even though it be turned to no further account, nor subserve any direct end... To open the mind, ... to refine it, ... to give it powers over its own facilities is an object as intelligible as the pursuit of virtue."

Despite the lack of evidence to support the connection between academic accomplishment and success in the workplace[2 3] the government and public equate examination passes with excellence. Many examinations in medicine seek to explore deep understanding of underlying concepts and do not try to test the ability to do a job. Recently there has been a move within general education towards learning and assessment that are focused on the ability of the learner to do the job. These changes towards "competency based education" are fundamental enough to amount to a paradigm shift in education. In this new educational model, assessment is by direct observation of competence. The issue was expressed clearly by Jessop: "Assessment of performance in the course of normal work offers the most natural form of evidence of competence and has several advantages, both technical and economic."[4]

The competency based training revolution began in the USA during the mid-1960s. The quality of teaching in schools was criticized and many felt that the curriculum for teacher training bore little relationship to the job requirements of teaching.[5] With federal government sponsorship several colleges began to teach student teachers according to a new competency based curriculum. This concentrated on skills for the classroom. Assessment became practice based and centred around observation of skills in action.[6]

In the UK during the early 1980s the idea of competency based training suited the government's thinking on education. There had been massive increases in youth unemployment and many employers felt that school leavers lacked the type of skills needed for work. Vocational education in the UK was compared unfavourably with that in other developed countries and government became convinced that reforms were needed. A succession of vocational courses, the New Training Initiative, Btec, NVQ and GNVQ has followed. Competence based learning appealed to the architects of these new qualifications. In the words of the Deputy Director of the National Council for Vocational Qualifications: "The measure of success for any education and training system should be what people actually learn from it, and how effectively. Just common sense you might think, yet this is a comparatively new idea."[4]

Vocational courses are concerned with teaching skills that have direct application in employment but many of its champions have sought to bring about a shift in education beyond this limited purpose. They see learning in terms of changes in behaviour. These changes are termed learning outcomes and are defined in a new type of syllabus which, instead of listing what is to be learned, concentrates on the skills, knowledge and understanding the learner will have at the end of the course. The new vocational curricula list learning objectives in great detail.

The competence model of the curriculum is linked to a new view of assessment. Traditionally a test is successful if it reliably returns a candidate's score in terms of a pass mark. Good teaching and learning leads to a pass in the test. In the new thinking the success of a test is defined in terms of how well a "pass" guarantees future good performance when the new knowledge is put to work. Clearly the examination hall has a reduced role in this type of testing and observation of the trainee in action becomes important. The expected outcomes of learning are defined as new competencies that can be assessed in action.

Medical education is vocational. Traditionally the curriculum has been academic in nature and a major emphasis in testing has been on traditional examinations. Practice has been taught alongside theory and efforts have been made to integrate the two to ensure the overall competence of graduates. New methods of teaching medical undergraduates have concentrated on learning outcomes in broader terms than success in academic examinations. Problem based learning is in some aspects a performance based approach to education. The curriculum concentrates on encouraging the skills of medical practice. Problem solving uses decision making skills and teachers hope to improve clinical reasoning. Learning outcomes are defined in terms of changed behaviour and assessment makes greater use of observation of behaviour. Learning and assessments are closely coupled and education is holistic. The use of competency teaching and assessment is now being promoted in medical education.[7]

So the tide is at the door and competency lead, performance based approaches to anaesthetic education are being seen. The *Objectives of Training in Anaesthesia* of the Australian and New Zealand College of Anaesthetists[8] are written in competency terms. The syllabus provided by the Royal College of Anaesthetists[9] is not as directly competence orientated but the changed emphasis is clear. So it seems the tide is not just at the door but already up to our necks. It is pertinent to wonder if anaesthetists understand what a change towards competence based learning implies.

Competence based learning will be associated with workplace competence testing. National examinations are intended to ensure that new entrants to specialist practice have reached an acceptable standard. They focus primarily on knowledge that can be tested by the type of assessments that are practicable, fair and consistent when applied to large groups of candidates.[10] Practical skills, behaviour and personal qualities are not amenable to formal examination testing. These qualities are none the less, important in determining if an anaesthetist is effective. Unfortunately practical clinical competence assessment is very difficult to perform. Assessment involves generalizing from an observation that has been made in the course of work; only if this generalization holds up in practice will the assessment be valuable. The sample of professional behaviour observed must be representative of all related behaviours.[11 12] Here is an immediate problem with the assessment of clinical competence. We do not know how wide a spectrum of behaviours we must observe in order to make valid overall conclusions.

A further difficulty is in deciding how to score an observation. An assessor can watch a trainee in action and then allocate a mark for competence. This approach is totally subjective and the assessments are likely to show poor reliability. Several approaches have been used to improve the objectivity of scoring. The examiner can score the trainee in several "domains". The scoring relies usually on a verbal rating between poor and very good. This approach at least indicates to the trainee the type of problems that the assessor is detecting. Greater consistency may be achieved by using a check list of observations that again can be related to domains. This makes some effort to ensure that the trainee is doing everything that should be done. An alternative means of conducting an observational assessment is by critical incident identification.[13] The trainee is observed and good and bad examples of practice are noted. A subsequent analysis of these according to predetermined criteria allows a score to be allocated. Modifications of Flanagan's technique which was originally developed for aircrew training have been used widely in medical[14–17] and nurse[18] education.

A more fundamental criticism of setting learning outcomes and then observing competencies is that this underrates the complexity of the professional task. Administering an anaesthetic can be divided into a sequence of competencies that are easy to see. Usually the trainee performs adequately in all steps of the sequence but this is no guarantee of competence. The progress of anaesthesia is not a succession of learned behaviours; it is based on complex cognitive skills expressed as clinical reasoning. Observing progress of anaesthesia does not easily reveal if the underlying reasoning is sound. The trainee may be running through an impoverished repertoire of behaviours and responses that are not flexible enough or deep enough to carry across into new situations. Sivarajan and colleagues found no correlation between clinical performance and knowledge in a spinal anaesthesia skill test.[19]

There is very little literature relating to the assessment of anaesthetists[20] and most of this makes no reference to how an observational assessment in the workplace can be done in ways that provide valid and reliable results. There is an obvious need for careful evaluation of available means of measuring clinical competence. It is necessary to develop tests that are reliable. This will not be easy. Even more important is consideration of the validity of the tests. There is a danger that competence testing will concentrate on the surface behaviour of the trainee without exploring the underlying soundness of decision making and the capacity for flexibility in a crisis. Any future changes in the training and assessment of anaesthetists must be based on correct understanding of what we learn, how we use that knowledge and how best it can be assessed. Until the time that research is done, measurements made in the workplace should not be used either to monitor the progress of trainees or make decisions in relation to their careers.

J. D. GREAVES
Newcastle School of Anaesthesia,
Royal Victoria Infirmary,
Newcastle upon Tyne NE1 4LP

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CLINICAL INVESTIGATIONS

Pharmacokinetic and clinical study of ropivacaine and bupivacaine in women receiving extradural analgesia in labour

A. F. McCrae, P. Westerling and J. H. McClure

Summary

We have compared, in a randomized, double-blind study, the pharmacokinetics of ropivacaine and bupivacaine during labour. Total and free plasma concentrations of ropivacaine and bupivacaine were measured after the first of two extradural doses. The main dose was 20 mg (test dose) and 30 mg, with a top-up dose of 25 mg when requested. After the main dose, $C_p$max (total) of ropivacaine (0.50 mg litre^{-1}) was similar to that of bupivacaine (0.48 mg litre^{-1}). At 20 min, $C_p$max (free) of ropivacaine (0.04 mg litre^{-1}) was higher than that of bupivacaine (0.02 mg litre^{-1}) (P=0.0025). The clinical effectiveness of the block was similar in both groups. (*Br. J. Anaesth.* 1997; **79**: 558–562).

Key words
Pharmacokinetics, ropivacaine. Pharmacokinetics, bupivacaine. Anaesthetics local, bupivacaine. Anaesthetics local, ropivacaine. Analgesic techniques, extradural. Analgesia, obstetric.

Ropivacaine (S-(-)-1-propyl-2', 6'-pipecoloxylidide hydrochloride monohydrate) is a long-acting amide local anaesthetic. It is closely related structurally to bupivacaine, but unlike bupivacaine, which is a racemic mixture, ropivacaine is the single S-enantiomer. Ropivacaine has pharmacodynamic and pharmacokinetic properties resembling those of bupivacaine in animals and humans,[1–3] but has less central nervous system toxicity and cardiotoxicity than bupivacaine.[4 5]

Initial clinical studies of extradural anaesthesia with ropivacaine indicated overall pharmacodynamic and pharmacokinetic properties comparable with those of bupivacaine.[6] In double-blind studies comparing ropivacaine and bupivacaine, onset and duration of sensory block and overall clinical efficacy of anaesthesia were similar. Most studies have found that the depth and duration of motor block were less with ropivacaine than bupivacaine when used in equal concentrations.[7–9]

In an early study of bupivacaine in ewes, cardiotoxicity was enhanced by pregnancy.[10] However, subsequent work failed to find a difference in toxicity between pregnant and non-pregnant ewes after bupivacaine or ropivacaine.[11] Both ropivacaine and bupivacaine are weak bases and are bound to α_1-acid glycoprotein (AAG) in plasma. The unbound (free) drug concentration is considered to be related to systemic pharmacodynamic and toxic effects.[12] Studies of ropivacaine in pregnant and non-pregnant ewes showed that pregnancy was accompanied by altered pharmacokinetics; total clearance of ropivacaine was lower in pregnant compared with non-pregnant ewes.[13]

The principal aim of this study was to investigate free and total plasma concentrations of ropivacaine or bupivacaine after an extradural dose of 50 mg, given to pregnant women in labour. The secondary aim was to assess central neural block and the safety of ropivacaine and bupivacaine in extradural analgesia in labour.

Patients and methods

This randomized, double-blind study was approved by the local Ethics Committee. Written informed consent was obtained before the study from 22 women in established labour, having regular painful contractions, and requesting extradural analgesia for pain relief. No previous analgesia other than nitrous oxide had been used. All patients were ASA I, at >36 weeks' gestation, with a singleton fetus in vertex presentation. Patients were allocated randomly to one of two matched treatment groups to receive ropivacaine or bupivacaine. Patients with a history of allergy to amide local anaesthetics, pre-eclampsia or drug abuse were excluded.

An i.v. infusion of Ringer's lactate was commenced and patients received up to 250 ml of fluid. A 16-gauge cannula was inserted into a vein in the contralateral antecubital fossa for blood sampling. After infiltration of the skin with 1% lignocaine, a 16-gauge Tuohy needle was inserted at the L2–3 interspace in the right lateral or sitting position and the extradural space identified with loss of resistance using less than 4 ml of saline. An end-holed catheter was inserted 3 cm in a cephalad direction. With the patient in the right lateral position and after negative aspiration tests for blood or CSF, a test dose of

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A. F. McCrae, MB, ChB, DRCOG, FFARCSI, J. H. McClure, BSc(Hons), MB, ChB, FRCA, Department of Anaesthetics, Royal Infirmary, Edinburgh EH3 9YW. P. Westerling, PhD, Astra Pain Control AB, S151-85 Sodertalje, Sweden. Accepted for publication: June 20, 1997.

20 mg (4 ml) of the study drug (0.5% bupivacaine or 0.5% ropivacaine from identically labelled coded ampoules identified only by number) was injected at a rate of 0.5 ml s^{-1}. Five minutes later, the patient was turned to the left lateral position and 30 mg (6 ml) of the same test solution were injected over 12 s. When additional analgesia was requested, a top-up injection of 25 mg (10 ml) of the test solution in a concentration of 0.25% was given, with the patient in the wedged supine position. When a second top-up was requested, the drug administration period was complete and the extradural was continued using bupivacaine or lignocaine as appropriate until delivery.

BLOOD SAMPLING

Samples of blood (5 ml) were obtained from the venous cannula for measurement of local anaesthetic concentrations immediately before drug administration, at time 0 (end of injection of main dose), at 10, 20 and 30 min, at 1 h (2 h if before topped up) and immediately before the top-up injection. At 20 min after the main injection, additional 5-ml samples were obtained for measurement of free drug concentrations and AAG. Samples were transferred from the syringe into heparinized test tubes. Plasma was separated by centrifugation for 10 min at 3000 rpm at room temperature within 2 h of collection, transferred to fresh tubes (Cryotube 5 ml, Nunc, Denmark) and stored in a freezer at −20 °C until analysis.

BIOANALYTICAL METHODS

Analysis was carried out at the Department of Bioanalysis, Astra Pain Control, Sweden. Total concentrations of ropivacaine and bupivacaine in plasma were measured using capillary gas chromatography with nitrogen sensitive detection after liquid–liquid extraction.[14] The limit of quantification (LOQ) was set at 0.010 mg $litre^{-1}$ and between-day precision for ropivacaine and bupivacaine during the study was 3–9% (relative SD, RSD) measured in the concentration range 0.02–2.00 mg $litre^{-1}$. Free concentrations of ropivacaine and bupivacaine in plasma were measured using coupled column liquid chromatography after ultrafiltration.[15] Ropivacaine and bupivacaine were detected by ultraviolet at 210 nm, and the LOQ was set at 0.003 mg $litre^{-1}$. Between-day precision during the study was 7% (RSD) for both ropivacaine and bupivacaine at a concentration of 0.030 mg $litre^{-1}$. Assay of AAG was performed using a radial immunodiffusion procedure with commercially prepared kits (NOR-Partigen, Behringwerkie, Marburg, Germany). LOQ was set at 2 μmol $litre^{-1}$ and between-day precision was greater than 9% (RSD).

CLINICAL EVALUATION

At 30 min after the main dose and top-up, assessments of the upper level of sensory block to pinprick were made using a short-bevelled 27-gauge dental needle (Monoject 401). Assessments of motor block were made using a modified Bromage scale: 0=no motor paralysis (full flexion of hip, knee and foot), 1=inability to raise extended leg (just able to move knee), 2=inability to flex knee (able to move foot only) and 3=inability to flex ankle joint (unable to move foot or knee). At the same times evaluation of the quality of analgesia was judged by the investigator as good, moderate or poor. Maternal heart rate and arterial pressure were measured before the extradural, at 5, 10, 15, 20 and 30 min after the main dose or top-up and at 30-min intervals during labour. Fetal heart rate was recorded continuously on a cardiotocograph during the study and values recorded at the same times as maternal cardiovascular variables. Hypotension was defined as a decrease in systolic arterial pressure to less than 90 mm Hg and bradycardia as a decrease in maternal heart rate to less than 50 beat min^{-1}.

The mode of delivery (spontaneous vertex, forceps, ventouse or Caesarean section) and Apgar scores of the newborn at 1 and 5 min were recorded. Mother and baby were visited daily during their hospital stay and adverse events were recorded. Patients were contacted by telephone 1–2 weeks after delivery for follow-up.

Individual free and total plasma concentrations of ropivacaine and bupivacaine were measured. Peak plasma concentrations (C_{p}max) and time to peak concentrations (tC_{p}max) were estimated. Differences in pharmacokinetic data were calculated using the Wilcoxon signed rank statistic. $P<0.05$ was considered statistically significant.

Results

Twenty-two patients were recruited. There were technical problems with two patients in the bupivacaine group (spoiled blood samples in one and failure to obtain all blood samples in the other) and these two patients were replaced. The results presented therefore are clinical data for 22 patients and pharmacokinetic data for 20 patients.

In the ropivacaine group, there were five primiparous and five multiparous women compared with eight and four, respectively, in the bupivacaine group. There were no differences in patient characteristics between the groups (table 1).

All patients received the main and top-up doses. The median time to first top-up was 111 min in the ropivacaine group and 126 min in the bupivacaine group.

Table 1 Patient characteristics (mean (SD) [range])

	Ropivacaine group (n=10)	Bupivacaine group (n=12)
Age (yr)	26.9[19–36]	27.8 [21–34]
Height (cm)	163.5 (3.9) [157-168]	161.9 (5.2) [155–170]
Weight (kg)	74.9 (6.1) [67–89]	74.5 (10.5) [59–99]
Primiparae/multiparae (n)	5/5	8/4

Table 2 $C_P$max (total) after the main dose of ropivacaine or bupivacaine, and total and free plasma concentrations (C_P) at 20 min. **$P<0.01$

			C_p at 20 min		
	$C_P$max (total) (mg litre^{-1})	tC_Pmax (min)	Total (mg litre^{-1})	Free (mg litre^{-1})	Bound (%)
Ropivacaine					
Mean	0.50		0.47	0.04**	91.8
SD	0.103		0.100	0.013	2.1
Median	0.53	25	0.49	0.03	92.3
Range	0.32–0.66	20–30	0.32–0.62	0.03–0.07	86.9–93.8
Bupivacaine					
Mean	0.48		0.47	0.02	95.6
SD	0.117		0.114	0.008	1.2
Median	0.44	20	0.43	0.02	95.8
Range	0.35–0.68	10–30	0.35–0.68	0.01–0.04	93.3–97.4

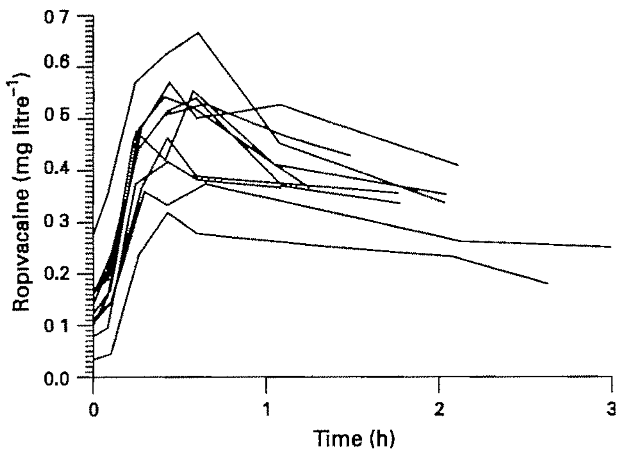

Figure 1 Plasma concentrations of total ropivacaine *vs* time.

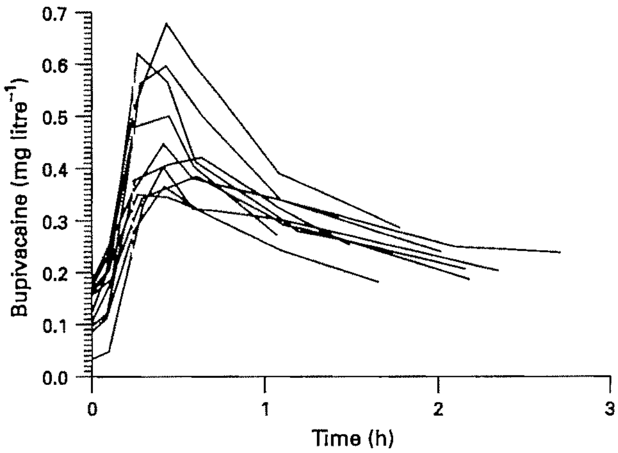

Figure 2 Plasma concentrations of total bupivacaine *vs* time.

PHARMACOKINETIC EVALUATION

Plasma concentrations of ropivacaine (fig. 1) and bupivacaine (fig. 2) up to the time of requesting the first (study drug) top-up are shown. All parturients received a top-up dose of the study drug.

After the main dose, mean $C_P$max (total) of ropivacaine was 0.50 mg litre^{-1} (95% Wilcoxon confidence intervals 0.42, 0.56 mg litre^{-1}) and mean $C_P$max (total) of bupivacaine was 0.48 (0.39, 0.56) mg litre^{-1}. Twenty minutes after the main dose, mean C_P (total) was the same in both groups (0.47 mg litre^{-1}), but the free concentration of ropivacaine (C_P (free)) was 0.04 (0.03, 0.05) mg litre^{-1}, significantly higher than that of bupivacaine (0.02 (0.02, 0.03) mg litre^{-1}) ($P=0.0025$) (table 2).

Protein binding of ropivacaine (mean 92%) was lower compared with bupivacaine binding (mean 96%). The concentration of AAG was similar in the two groups, ranging from 9 to 19 μmol litre^{-1}, but there was a higher free fraction of ropivacaine than bupivacaine (fig. 3).

CLINICAL EVALUATION

The following results are described for 10 patients in the ropivacaine group and 12 in the bupivacaine group.

Sensory and motor block

Maximum segmental spread of sensory block after the main dose was T6–11 in the ropivacaine group and T4–11 in the bupivacaine group. After the top-up, spread was T7–10 in the ropivacaine group and T4–11 in the bupivacaine group. Motor block in the ropivacaine group was grade 0 in four and grade 1 in six patients after the main dose and grade 0 in two, grade 1 in six and grade 2 in two after ropivacaine top-up. In the bupivacaine group, motor block was grade 0 in five, grade 1 in six and grade 2 in one after the main dose and grade 0 in five, grade 1 in five and grade 2 in two after bupivacaine top-up (table 3).

Table 3 Motor block (Bromage scale)

	Ropivacaine (n=10)		Bupivacaine (n=12)	
	Main dose	Top-up	Main dose	Top-up
Grade 0	4	2	5	5
Grade 1	6	6	6	5
Grade 2	0	2	1	2
Grade 3	0	0	0	0

Quality of analgesia

This was assessed by the investigator 30 min after the main dose and was considered good in nine of 10 patients in the ropivacaine group and in 10 of 12 in the bupivacaine group. After the top-up, analgesia was good in nine of 10 in the ropivacaine group and in nine of 12 patients in the bupivacaine group.

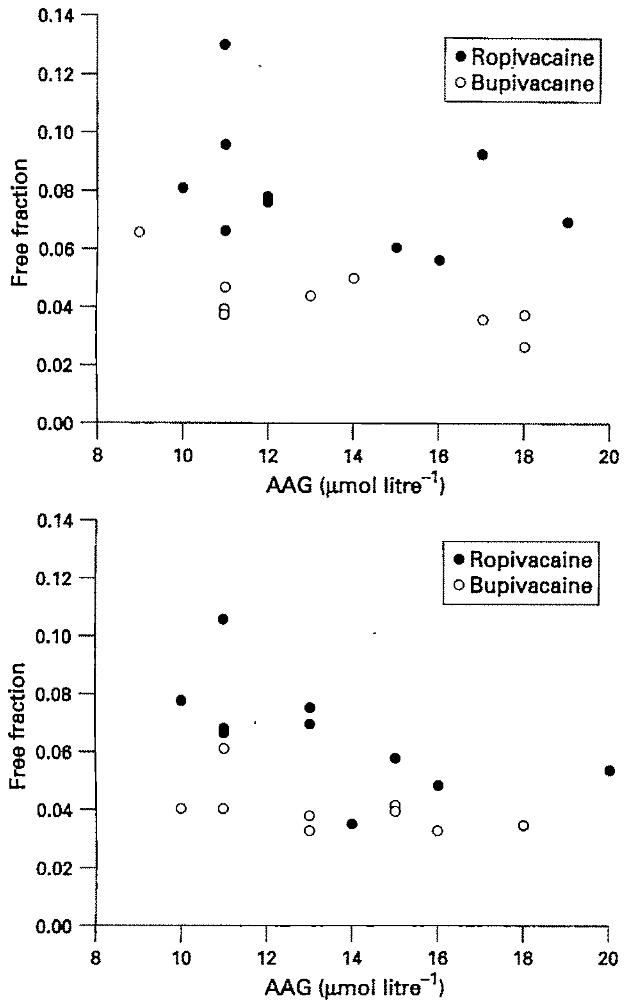

Figure 3 Free fraction of ropivacaine and bupivacaine *vs* plasma concentrations of α_1-acid glycoprotein (AAG) after the main dose.

Neonatal assessments

In the ropivacaine group, six patients delivered spontaneously, three required forceps and one patient had a Caesarean section for failure to progress. In the bupivacaine group, seven patients had spontaneous deliveries and five required forceps delivery. Apgar scores were >7 for all babies at 5 min.

Cardiovascular changes

There were no obvious differences between the groups in systolic or diastolic arterial pressures. In both groups there was a decrease in arterial pressure 10–20 min after the main dose and top-up. In each group, three patients became hypotensive. Two patients in the ropivacaine group were treated with ephedrine, but no patient in the bupivacaine group required ephedrine. There were two episodes of transient fetal bradycardia in each group, but no evidence of fetal distress.

Discussion

In this study, $C_p$max (total) after the main dose was similar for ropivacaine and bupivacaine. Other studies in animals[3] and patients[9 16] comparing extradural ropivacaine with bupivacaine have found higher $C_p$max (total) values for ropivacaine. This could be because of the higher lipid solubility and higher tissue protein binding of bupivacaine which binds to neural tissue and fat in the extradural space and therefore may have a lower rate of absorption. However, a study comparing the two drugs as extradural anaesthesia for Caesarean section[17] and a study in intercostal blocks[18] comparing the two agents found no difference in $C_p$max (total).

We found that the free concentration of ropivacaine (0.04 mg litre^{-1}) was greater than bupivacaine 20 min after the main dose (0.02 mg litre^{-1}). A higher free concentration of ropivacaine compared with bupivacaine was also found in studies of continuous extradural infusion in labour[16] and after a 150-mg extradural dose for Caesarean section.[17]

Basic drugs such as amide local anaesthetics are bound in plasma by AAG, which is an acute phase protein, and concentrations vary in disease states, trauma and after surgery. Protein binding of ropivacaine (92%) was less than bupivacaine (96%). It has been found that as the serum concentration of ropivacaine or bupivacaine increases, protein binding decreases.[11]

Plasma protein binding is not relevant to systemic toxicity when caused by accidental i.v. injection because the mass of plasma protein in the volume of blood exposed to the drug is overwhelmed, leaving a significant mass of unbound drug available for diffusion into the excitable tissue of the central nervous system and the heart.[19]

Local anaesthetic toxicity is related to free drug concentration.[12] It has been shown in sheep, using i.v. infusion of ropivacaine or bupivacaine, that there is no significant difference in the total serum concentration of each drug in pregnant and non-pregnant ewes at the onset of local anaesthetic toxicity. However, the dose of ropivacaine required to produce that serum concentration was 40–50% higher than the corresponding dose of bupivacaine. It was observed that in the pregnant sheep the free concentration of ropivacaine was greater than that of bupivacaine at the time of cardiovascular collapse.[11]

The higher free concentrations of ropivacaine compared with bupivacaine after extradural administration of similar doses during labour reflects the lower lipid solubility and binding of ropivacaine by plasma proteins. These observations were not accompanied by any adverse effects on the mother or fetus at the doses given in this study.

The total area under the plasma concentration *vs* time curve (AUC) and the apparent disposition half-life ($T_{1/2}$) could not be estimated because of too few sampling times and confounding factors such as additional top-ups, mostly with bupivacaine, and the different timings between extradural block and delivery.

Clinically, the effects of the two drugs were similar in terms of sensory and motor block during extradural analgesia in labour, as has been found in other studies.[20 21] There was no difference in the mode of delivery and no difference between the drugs in terms of motor block, as assessed by the

Bromage scale, at the doses given. The modified Bromage scale assesses both spread and intensity of motor block. It may not be sensitive enough to quantify differences in the intensity of motor block in the limited segmental spread in extradural analgesia in labour.

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Magnetic resonance imaging of the extradural space of the thoracic spine

Y. HIRABAYASHI, K. SAITOH, H. FUKUDA, T. IGARASHI, R. SHIMIZU AND N. SEO

Summary

To clarify the anatomy of the extradural space of the thoracic spine, we have compared magnetic resonance (MR) images of the thoracic spine with those of the lumbar spine. In 20 healthy volunteers, T2-weighted axial MR images were obtained at the levels of the C7–T1, T7–8, T11–12 and L2–3 vertebrae. The posterior extradural space seen in the slice through the intervertebral disc varied in shape and size depending on the vertebral level, and the shape of the space converted from triangular to crescent-shaped on moving from the lumbar to the thoracic spine. In particular, the posterior extradural space was almost absent at the C7–T1 level, indicating that the posterior extradural fat was rudimentary or non-existent at the thoracocervical level. At this level, the dura mater seemed to be in direct contact with the ligamentum flavum. Segmentation of the posterior extradural space was commonly observed at the L2–3 and T11–12 levels; however, incomplete segmentation of the posterior extradural space was often present at the T7–8 level. (*Br. J. Anaesth.* 1997; **79**: 563–566).

Key words

Anatomy, extradural space. Measurement techniques, magnetic resonance imaging.

Understanding of the anatomy of the extradural space is the key to successful introduction of extradural catheters and medicines. Because extradural anaesthesia and analgesia is most frequently performed at the lumbar vertebral level, the anatomical study of the extradural space has been studied extensively at this level.[1-5] With respect to other vertebral levels, including the thoracic and cervical levels, however, few studies have been conducted.[6] The anatomical characteristics of the spine are significantly different between the thoracic and lumbar spine, and thus the anatomy of the extradural space may differ according to the vertebral level. Magnetic resonance (MR) imaging provides detailed information on the anatomy of the extradural space in living subjects.[1 7] To understand the anatomy of the extradural space at the thoracic vertebral level, we have compared MR images of the thoracic spine with those of the lumbar spine.

Subjects and methods

The Institutional Review Board approved our study, and informed consent was obtained from all subjects. We studied 20 healthy Japanese volunteers (14 men), aged 21–41 yr (median 28 yr). Mean weight, height and body mass index were 64 (range 47–85) kg, 167 (153–182) cm and 23 (19–28) kg m^{-2}, respectively. Subjects with lumbago or previous spinal surgery were excluded. MR imaging examinations were performed with the subject in the supine position. At the levels of the C7–T1, T7–8, T11–12 and L2–3 vertebrae, T2-weighted axial MR images were obtained using an MR imaging system (VISART/Progress, Toshiba Corporation, Tokyo, Japan) operating at 1.5 T. Technical specifications included a repetition time of 4000–5500 ms, echo time of 100 ms, slice thickness of 4 mm, number of slices 9–11 and a field of view of 20 cm. Measurements taken from the MR images included the area of the dural sac, sagittal and transverse diameters of the dural sac, anteroposterior dimension of the fat-filled posterior extradural space, and distance from the skin to the posterior extradural space. The area was measured using a digital planimeter (KP-90N, Uchida Yoko Ltd, Tokyo, Japan).

Data were analysed using ANOVA for differences among the four levels of the spine. If significant differences were observed, the Bonferroni test was used for *post hoc* analysis. Data for men and women were compared using the unpaired t test. $P<0.05$ was considered statistically significant.

Results

The axial slice through the intervertebral disc showed that the posterior extradural space was enclosed by the ligamentum flavum, articular capsule and the dura. The fat in the posterior extradural space, having a high signal and being uniform (white), appeared as a triangle, typically at

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YOSHIHIRO HIRABAYASHI, MD, KAZUHIKO SAITOH, MD, HIROKAZU FUKUDA, MD, TAKASHI IGARASHI, MD, REIJU SHIMIZU, MD, Department of Anaesthesiology, Jichi Medical School, Tochigi, 329-04 Japan. NORIMASA SEO, MD, Department of Anaesthesia and Intensive Care, Omiya Medical Centre, Jichi Medical School, Omiya, Saitama, 330 Japan. Accepted for publication: June 10, 1997.

Correspondence to Y. H.

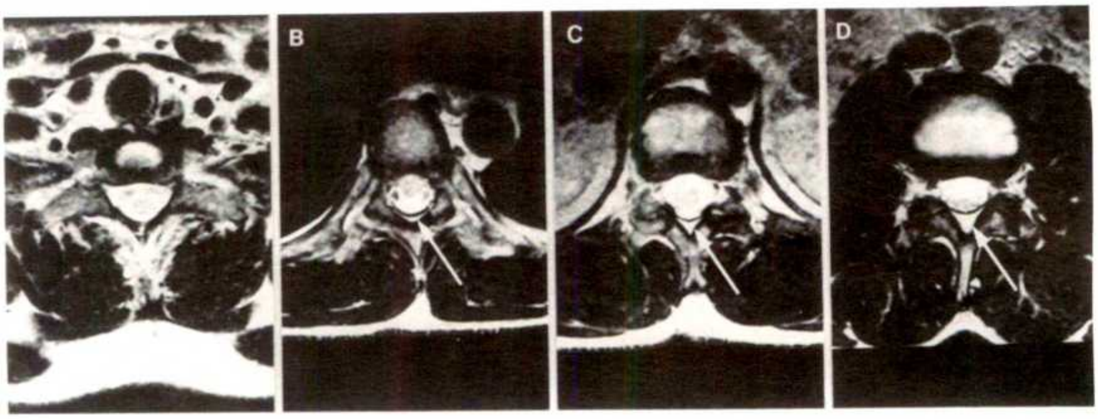

Figure 1 T2-weighted MR imagings showing the axial slice through the intervertebral disc at the C7–T1 (A), T7–8 (B), T11–12 (C) and L2–3 (D) levels. The arrows indicate the posterior extradural fat which has a high signal and is uniform. The shape of the fat converts from triangluar (C) to crescent-shaped (B) on moving from the lumbar to the thoracic spine. There is no posterior extradural fat at the thoracocervical junction (A).

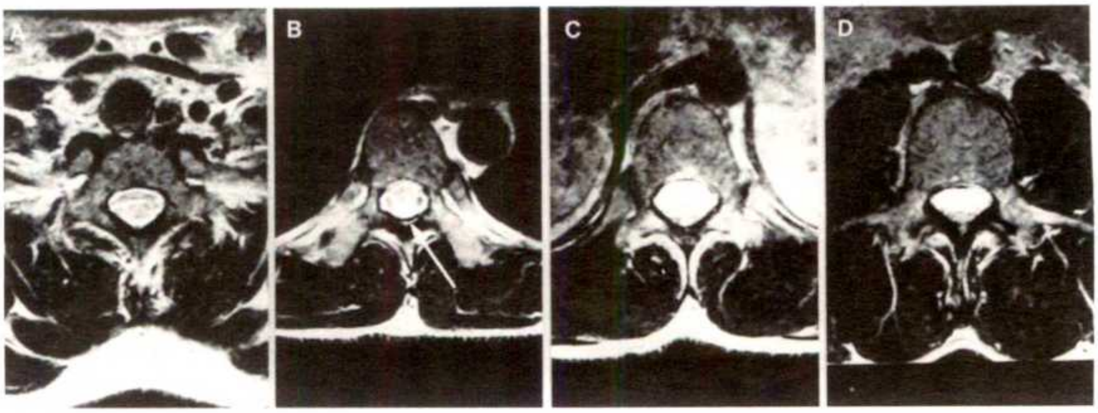

Figure 2 T2-weighted MR imagings showing the axial slice through the pedicles at the C7–T1 (A), T7–8 (B), T11–12 (C) and L2–3 (D) levels. The arrow shows the posterior extradural fat. The posterior extradural fat found only at the mid-thoracic level (B) indicates that the posterior extradural space at the mid-thoracic spine extends from one compartment to the next.

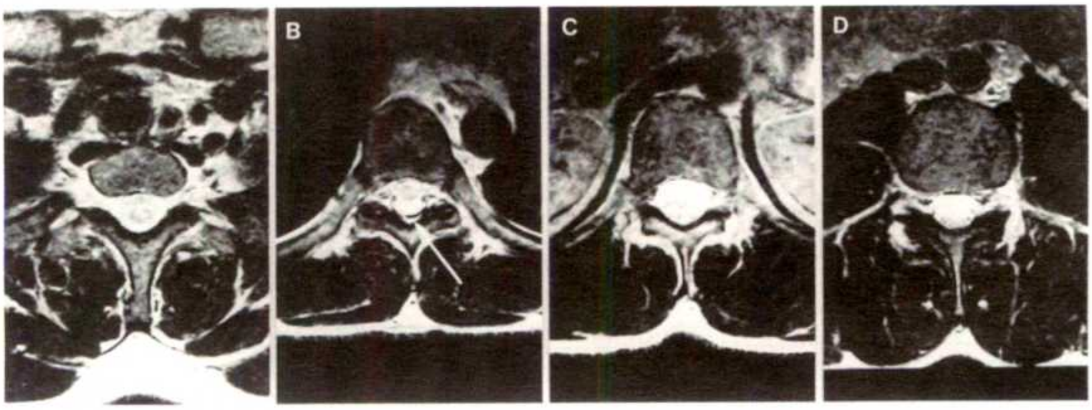

Figure 3 T2-weighted MR imagings showing the axial slice through the lamina at the C7–T1 (A), T7–8 (B), T11–12 (C) and L2–3 (D) levels. The arrow indicates the posterior extradural fat which lies between the dura and lamina at the level of the rostral lamina. The posterior extradural fat is found only at the mid-thoracic level (B).

the lumbar spine (fig. 1D). The fat-filled posterior extradural space varied in shape and size depending on the vertebral level. The shape of the space converted from triangular (fig. 1C) to crescent-shaped (fig. 1B) on moving from the lumbar to the thoracic spine. The anteroposterior dimension of the fat-filled posterior extradural space was shorter at the thoracic levels than at the lumbar level ($P<0.001$) (table 1). The fat-filled posterior extradural space appeared as a thin crescent at the T7–8 level in all subjects (fig. 1B); however, at C7–T1, the space was almost absent (fig. 1A), indicating that the posterior extradural fat was rudimentary or non-existent at the thoracocervical level.

In contrast with the axial slice through the intervertebral disc, as a rule no posterior extradural fat was evident in the axial slice through the pedicles (fig. 2) and lamina (fig. 3). This indicated that the

Table 1 Measurements taken from MR images at the C7–T1, T7–8, T11–12 and L2–3 levels (mean (SD) [range]). $^{**}P<0.01$, $^{***}P<0.001$ (Bonferroni test) *vs* L2–3

	C7–T1	T7–8	T11–12	L2–3
Area of the dural sac (cm^2)	1.7 (0.3) [1.2–2.3]	1.6 (0.3) [1.2–2.2]	1.8 (0.4) [1.2–2.4]	1.8 (0.3) [1 3–2.4]
Transverse diameter of the dural sac (mm)	17.5 (1.7) [14–21]	16.6 (1.8) [13–19]***	16.7 (2.3) [13–21]**	18.4 (1.9) [16–22]
Sagittal diameter of the dural sac (mm)	12.3 (1.1) [10–15]	13.4 (1.2) [11–16]	13.8 (1.8) [11–17]**	12.5 (1.2) [11–15]
Anteroposterior dimension of the posterior extradural space (mm)	0.4 (0.9) [0–3]***	2.6 (1.3) [0–5]***	4.1 (1.1) [3–6]***	7.1 (1.3) [4–9]
Distance from the skin to the posterior extradural space (mm)	55.4 (8.2) [41–73]***	36.7 (4.3) [30–44]	35.9 (5.9) [26–46]	38.2 (6 3) [27–48]

Table 2 Comparison between men and wemen for measurements taken from MR images at the C7–T1, T7–8, T11–12 and L2–3 levels (mean (SD) [range]). $^{*}P<0.05$, $^{**}P<0.01$ (unpaired *t* test) *vs* women

	Sex	C7–T1	T7–8	T11–12	L2–3
Area of the dural sac (cm^2)	Men	1.7 (0.3) [1.2–2.3]*	1.7 (0.3) [1.2–2.2]	1.8 (0.4) [1.2–2.3]	1.8 (0.3) [1.3–2.5]
	Women	1.5 (0.1) [1.4–1.7]	1.6 (0.2) [1.4–1.9]	1.9 (0.6) [1.2–2.4]	1.8 (0.4) [1.4–2.3]
Transverse diameter of the dural sac (mm)	Men	18.1 (1.6) [14–21]**	15.8 (2.1) [13–19]	16.4 (2.1) [13–19]	18.4 (1.7) [16–22]
	Women	16.0 (0.8) [15–17]	15.3 (0.8) [14–17]	17.1 (2.9) [13–21]	18.4 (2.3) [16–22]
Sagittal diameter of the dural sac (mm)	Men	12.5 (1.1) [10–15]	13.6 (1.3) [11–16]	13.8 (1.8) [11–17]	12.5 (1.1) [11–14]
	Women	11.7 (0.8) [11–13]	13.0 (1.0) [12–15]	13.8 (1.8) [11–15]	12.8 (1.4) [11–15]
Anteroposterior dimension of the posterior extradural space (mm)	Men	0.4 (1.0) [0–3]	2.8 (1.0) [1–5]	4.1 (1.1) [3–6]	7.2 (1.5) [4–9]
	Women	0.3 (0.8) [0–2]	2.0 (1.7) [0–5]	4.0 (1.0) [3–5]	7.0 (0.7) [6–8]
Distance from the skin to the posterior extradural space (mm)	Men	57.3 (7.8) [41–73]	37.0 (4.1) [30–44]	37.6 (4.5) [29–46]*	40.0 (5.4) [33–48]*
	Women	50.9 (7.8) [41–62]	35.8 (4.9) [31–44]	31.9 (7.4) [26–46]	34.1 (6.7) [27–42]

posterior extradural compartment was discontinuous, separated by areas of contact of the dura with the rostral lamina. At the level of the rostral lamina, no posterior extradural fat was present at T11–12 (fig. 2C, 3C) and L2–3 (fig. 2D, 3D), or at C7–T1 (fig. 2A, 3A) in any subject. With respect to T7–8, however, the posterior extradural fat was often identified even at the levels of the pedicles (fig. 2B) and lamina (fig. 3B), indicating that the fat in the posterior extradural space at the mid-thoracic spine extended from one compartment to the next between the dura and lamina.

Significant differences between men and women were noted only at the C7–T1 level for measurements of the dural sac (table 2). There were no differences between men and women for measurements at the other three levels of the spine. The distance from the skin to the extradural space was greater in men than in women in the low thoracic and lumbar regions ($P<0.05$).

Discussion

Increasing evidence indicates that the extradural space is divided into posterior, anterior and lateral compartments by areas where bone and ligament are in contact with dura,[3 8] although traditional teaching describes this space as a circumferential structure. These three compartments distribute segmentally around the dural sac. The posterior extradural space is the space into which the needle and catheter enters during extradural anaesthesia, and hence understanding of the anatomy of the posterior extradural space is the key to successful block.[9] The posterior extradural space contains chiefly fat which appears as a high signal on T2- weighted MR images. The fat within this space may follow the margin of the posterior extradural space. The findings of this study showed that the posterior extradural fat significantly varied in shape and size depending on the vertebral level. The shape of the posterior extradural fat changed from triangular to crescent-shaped on moving from the lumbar to the thoracic spine. At the thoracocervical junction, posterior extradural fat was almost absent. These findings may suggest that the effective capacity of the posterior extradural space reduces on passing from the lumbar to the thoracic level. The progressively diminishing posterior extradural fat in levels cephalad from the lumbar spine may, in part, explain the smaller anaesthetic dose requirements at the thoracic and cervical regions than in the lumbar region.

In the low-thoracic and lumbar vertebral level, the posterior extradural fat was present in the axial slice through the intervertebral disc but not in the axial slices through the pedicles and lamina, which may suggest that the posterior extradural compartment is discontinuous, separated by areas of contact of the dura with the rostral lamina. The mid-thoracic spine, however, often showed a continuous layer of posterior extradural fat which extended between the dura and lamina even at the level of the rostral lamina. This indicated that the fat in the posterior extradural space at the mid-thoracic spine extended from one compartment to the next between the dura and lamina. Incomplete segmentation of the posterior extradural compartment observed in our MR images was confirmed by the recent observations of Hogan who examined the cryomicrotome section of the spine from cadavers.[6] The author demonstrated that incomplete segmentation of the posterior extradural compartment frequently occurs at the mid- and upper thoracic levels. Incomplete segmentation of the posterior extradural space at thoracic levels may, in part, explain the fact that catheters are easily inserted for a far longer distance without kinking in the thoracic than in the lumbar region.[10]

Textbooks describe the anteroposterior dimension of the posterior extradural space in the lumbar region as 5–6 mm[11] or 4–6 mm.[12] Nickallis and Kokri reported that the mean value of the dimension in the lumbar region was 6.8 (SD 1.9) mm.[13] Bevacqua, Haars and Brand published a value of 6.9 (4) mm.[9] Our study showed that the value of the anteroposterior dimension of the posterior extradural space at the L2–3 interspace was 7.1 (1.3) mm, which does not differ significantly from those published previously. With respect to the thoracic region, however, few studies have been conducted on the size of the extradural space.[12] The values reported in our study are, to our knowledge, the first measurements by MR imaging. In a recent detailed study of cryomicrotome section of the thoracic spine, the anteroposterior dimension of the posterior extradural space was not measured.[6]

The diminished anteroposterior dimension of the posterior extradural space in the upper and mid-thoracic spine suggests an increased incidence of unintentional dural perforation during extradural puncture. However, Giebler, Scherer and Peters reported that unintentional dural perforation was observed significantly less in the mid- and upper thoracic regions in 4185 patients receiving thoracic extradural catheterization.[14] Tanaka and colleagues also reported significantly less unintentional dural perforations in the cranial vertebral regions compared with the lower thoracic and lumbar regions.[15] Thoracic extradural procedures are usually attempted by clinicians with considerably more experience whereas new trainees usually start with patients requiring the lumbar approach, and thus there may well be a learning curve. In addition, in the mid-thoracic region, the laminae overlap and angulation of the spinous processes is steep. Consequently, cephalad angulation of the needle is required during insertion. This cephalad angulation produces a longer oblique course across the extradural space and may compensate for the diminished anteroposterior dimension of the posterior extradural space.[6] This obligatory angle also makes the blunt back surface of the Tuohy needle face the dura.

This study was performed in subjects of Japanese origin. All of our volunteers were of relatively small stature and weight compared with European or North American subjects, and hence the results of this study can be applied directly only to subjects of the same race and within the same age, stature and weight range of those in this study. In addition, the number of volunteers examined in this study was so small that definitive conclusions on the differences between men and women cannot be reached.

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Pharmacokinetic–pharmacodynamic modelling of the EEG effects of Ro 48-6791, a new short-acting benzodiazepine, in young and elderly subjects

J. DINGEMANSE, J. HÄUSSLER, W. HERING, H. IHMSEN, S. ALBRECHT, M. ZELL, H. SCHWILDEN AND J. SCHÜTTLER

Summary

The objectives of this study were to explore, by a modelling approach, in nine young (24–28 yr) and nine elderly (67–81 yr) male subjects, the pharmacokinetics and pharmacodynamics of Ro 48-6791, a new water soluble benzodiazepine. A microprocessor-controlled i.v. infusion pump generated linearly increasing arterial plasma concentrations until predetermined EEG and clinical end-points were attained. This concentration was maintained for 15 min and thereafter the infusion was discontinued. Haemodynamic and respiratory variables were monitored continuously. At full reorientation of the subject, a second infusion cycle was started under the same conditions to investigate the reproducibility of the concentration–effect relationship. The plasma concentration–time profiles of Ro 48-6791 were fitted accurately to an open three-compartment model. Plasma concentrations of Ro 48-6792, an N-dealkylated metabolite, accumulated during the course of the study. Pharmacokinetic variables of Ro 48-6791 were similar for both groups. The largest differences between young and elderly subjects, respectively, were found for clearance (mean 85 (SD 23) *vs* 71 (15) litre h^{-1}) and k_{12} (11 (7) *vs* 7 (3) h^{-1}). The concentration–median EEG frequency relationship was described with a sigmoid Emax model. Elderly subjects showed slightly increased drug sensitivity compared with young subjects (EC_{50} 72 (25) and 44 (15) μg $litre^{-1}$ in young and elderly subjects, respectively). The concentration–response data of the second infusion cycle deviated from the fitted curve suggesting either development of acute tolerance to the EEG effects of Ro 48-6791 or a role for drug metabolites. Because of the differences in sensitivity and clearance, lower doses of Ro 48-6791 should be administered to elderly compared with young subjects in order to achieve similar effects. (*Br. J. Anaesth.* 1997; **79**: 567–574).

Key words

Hypnotics benzodiazepine, Ro 48-6791. Pharmacokinetics, Ro 48-6791. Pharmacodynamics, Ro 48-6791. Age factors. Monitoring, electroencephalography.

Benzodiazepines are in widespread use as sedative–hypnotic agents.[1] Parenteral midazolam and other benzodiazepines are currently the most frequently used sedatives for conscious sedation.[2] Midazolam is also in widespread use for both induction and maintenance of general anaesthesia[3] and it is frequently administered for long-term sedation of critically ill patients in intensive care units.[4]

Midazolam is considered by many practitioners to be associated with a longer duration of action and greater inter-individual variability of effect than is desirable.[5 6] A sedative drug with the advantages of midazolam but with a shorter duration of action and less variability would be of great benefit.

Ro 48-6791 (3-(5-dipropylaminomethyl-1,2,4-oxadiazol-3-yl)-8-fluoro-5-methyl-5,6-dihydro-4H-imidazo [1,5-a]$^{1\,4}$ benzodiazepin-6-one) (fig. 1) is a new water soluble full agonist at the benzodiazepine receptor. In the first study in humans, in which doses of 0.1–3 mg were given i.v. over 20 min, Ro 48-6791 was shown to be well tolerated and to elicit dose-dependent central nervous system depressant effects.[7] An integrated pharmacokinetic–pharmacodynamic approach[8] applying neurophysiological effect measures (saccadic eye movements and electroencephalography β-power) provided pivotal data for further clinical development of Ro 48-6791. The compound had a comparable onset and duration of action to midazolam but was approximately five-fold more potent[7] and its volume of distribution and plasma clearance were larger than those of midazolam. The monopropyl metabolite Ro 48-6792 (fig. 1) rapidly appeared in plasma and seemed to have a longer elimination half-life than the parent compound.

The objectives of this study were to investigate in

JASPER DINGEMANSE*, PHD, Department of Clinical Research, F. Hoffmann-La Roche, Basel, Switzerland and Jacor Research, Bottmingen, Switzerland. JÜRGEN HAUSSLER, MD, MANFRED ZELL, MSC, Department of Clinical Research, F. Hoffmann-La Roche, Basel, Switzerland. WERNER HERING, MD, HARALD IHMSEN, MSC, SVEN ALBRECHT, MD, JÜRGEN SCHÜTTLER, MD, Department of Anaesthesiology, University of Erlangen, Erlangen, Germany. HELMUT SCHWILDEN, MD, PHD, Department of Anaesthesiology, University of Bonn, Bonn, Germany. Accepted for publication: July 14, 1997.

*Address for correspondence: Jacor Research, Buchenstrasse 2, 4103 Bottmingen, Switzerland.

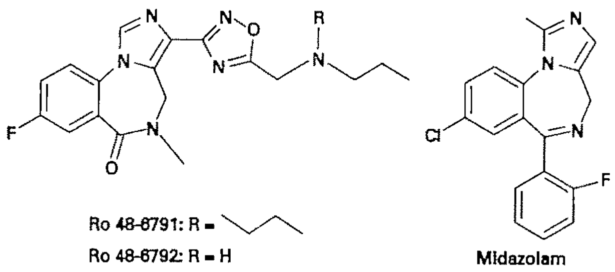

Figure 1 Chemical structures of Ro 48-6791 and its N-dealkylated metabolite Ro 48-6792. The structure of midazolam is given for comparison.

both young and elderly subjects the pharmacokinetics and pharmacodynamics of Ro 48-6791 in a concentration range for potential use in anaesthesia rather than conscious sedation. Arterial blood samples were collected during and after linearly ascending blood concentrations to exploit the advantages of pharmacokinetic–pharmacodynamic modelling approaches.[9 10] After recovery from the effects of the first infusion cycle, the drug was again infused until the same predetermined pharmacodynamic end-point was reached. This strategy was designed to evaluate the potential contribution of the metabolite Ro 48-6792 to the overall drug effects.

Subjects and methods

We studied 18 male subjects, nine young (age 24–28 yr, weight 66–89 kg) and nine elderly (age 67–81 yr, weight 71–90 kg), regarded as healthy on the basis of medical history, physical–neurological examination, 12-lead ECG and clinical laboratory measurements. Subjects were non-smokers and absence of drug abuse (including benzodiazepines) was verified by urinary screening. Three elderly subjects were receiving antihypertensive drugs and one was also receiving treatment for chronic heart failure. All subjects gave written informed consent before any screening procedures were performed. The study was approved by the Medical Ethics Review Committee of the Medical Faculty of the University of Erlangen, Erlangen, Germany.

STUDY DESIGN

All 18 subjects received treatment with Ro 48-6791. For safety reasons, the young subjects were treated before the elderly subjects. Commonly, two subjects were treated on one day. Subjects fasted for at least 8 h before the start of administration of the study drug until full orientation after the second infusion cycle. To avoid hypoglycaemia, Ringer's solution with glucose was infused during the study. The drug was given i.v. with a microprocessor-controlled (Toshiba 1850 C) infusion pump (Braun Perfusor fm, Braun, Melsungen, Germany) yielding linearly increasing plasma concentrations. The infusion rate was programmed to generate an increase in plasma concentration of 180 and 90 μg litre^{-1} h^{-1} in the young and elderly subjects, respectively. The slope of the plasma concentration increase in the elderly was reduced for safety reasons and anticipated increased drug sensitivity.[11 12] Pharmacokinetic variables obtained in the entry-into-human study[7] were used to program the software (IVA-PUMP, version 3.5., Erlangen, Germany). The study drug was infused until the median electroencephalographic (EEG) frequency was less than 4 Hz and the subject ceased to respond to a standardized loud acoustic stimulus. The concentration at which the sedation criteria were fulfilled was maintained for another 15 min before the infusion was terminated. As soon as the subject was fully oriented with regard to person, place and time, a second infusion cycle was started under the same conditions and with the same assessments.

PROCEDURES AND ASSESSMENTS

After ulnar artery blood supply had been examined by the Allen test, a cannula (Arrow, 20-G) was inserted by the Seldinger technique under local anaesthesia (Scandicain 1%, Astra Chemicals) into the radial artery of the non-dominant arm. Another cannula (Viggo, 18-G) was inserted into a forearm vein of the contralateral side for infusion of drug and glucose solution. Haemodynamic and EEG monitoring devices were installed and after a rest of approximately 10 min, stable baseline values of arterial pressure, heart rate, oxygen saturation and EEG were recorded.

Safety and tolerability

Adverse events were assessed by spontaneous reports, observations and questioning at regular intervals. The intensity of the adverse event was rated on a three-point scale (mild, moderate, severe). Systolic, diastolic and mean arterial pressures, and heart rate were monitored continuously via an arterial cannula (Sirecust 1281, Siemens) and the ECG was monitored continuously (Sirecust 1281, Siemens). Oral body temperature was measured just before start of the first infusion cycle, once during each period of constant plasma concentration and at the time of full orientation after the second cycle. Respiratory function was monitored continuously by pulse oximetry. When oxygen saturation decreased to less than 93% and 87% in young and elderly subjects, respectively, oxygen was administered by mask at a flow rate of 3–4 litre min^{-1}. During the phases of constant plasma concentration, an arterial blood sample was analysed for blood-gas tensions (BMS SMK2, Radiometer Copenhagen). After termination of the study, a physical examination and routine clinical laboratory tests were performed again.

Analytics and pharmacokinetics

Blood samples of 2.5 ml were collected into Monovettes containing EDTA as anticoagulant via the indwelling arterial cannula. The dead space of the cannula (approximately 300 μl) was flushed with a small amount of physiological saline after each blood sample. Before obtaining each sample for analysis, 1 ml of blood was obtained and discarded. The two infusion cycles were divided into two periods, periods A and B, and periods C and D, respectively. Period A was the first infusion period (including the plateau phase) followed by period B, the first recovery period, terminated by complete reorientation of the volunteer. Periods C and D were the respective phases of the second infusion cycle. During periods A and C, blood samples were obtained every 3–5 min. During periods B and D, blood was collected at increasing intervals of 2–30 and 2–60 min, respectively. In general, blood samples were collected for up to 6 h after termination of the second infusion with a total blood loss of approximately 160 ml per subject. After centrifugation, plasma samples were stored at −20 °C until analysis.

After precipitation of plasma proteins with acetonitrile, Ro 48-6791 and its metabolite Ro 48-6792 were extracted simultaneously from the supernatant on a trapping column using on-line solid phase extraction and separated on an analytical column with column-switching liquid chromatography. The effluent from the analytical column was passed directly to an ion spray interface coupled to a tandem mass spectrometer (LC-MS/MS). Mass spectrometric detection of the analytes was performed using selected reaction monitoring. Mean precision (coefficient of variation) and accuracy (percentage of real concentration present) for Ro 48-6791 and Ro 48-6792 in the concentration range 1.0–50 μg litre^{-1} were 6.1% and 101.7%, and 6.9% and 99.7%, respectively. The lower limit of quantification for both Ro 48-6791 and Ro 48-6792 was 0.5 μg litre^{-1}, using a 0.1-ml aliquot of plasma. Pharmacokinetic variables were calculated using standard techniques[13] and fitted to an open three-compartment model using the program NONMEM.[14]

Pharmacodynamics

EEG recording began 10 min before administration of Ro 48-6791 and was continued until the early second recovery period when subjects had regained full orientation. The EEG was recorded using the CATEEM electrodiagnostic monitoring system (Computer Aided Topographical Electro-encephalometry, Medisyst, Linden, Germany). Bipolar cerebral activity was acquired using an electro-cap (Electro-Cap, Electro-Cap International, Eaton, OH, USA) with the electrodes positioned according to the international 10–20 system and using Cz as reference. The gap between the cavities of the electrodes and the tissue was bridged by an electrolytic jelly. The signals were preamplified with a battery-powered amplifier close to the head and the resulting digital code was transmitted by optical fibre to the CATEEM system. Artefact-free serial epochs of 4 s were digitized at a rate of 512 Hz (12 bit) using bandpass filters between 0.45 and 35 Hz. The high input impedance ensured a sufficient signal-to-noise ratio with electrode impedances ranging from 1 to 100 kΩ. An additional display of the unprocessed raw EEG was used to check the variables derived. For each lead, EEG analysis included changes within individual band power and median frequency, defined as the frequency which divides the area below the power spectrum curve into two equal parts. The individual frequency bands were set as follows: delta 1.25–4.5 Hz, theta 4.75–6.75 Hz, alpha$_1$ 7.0–9.5 Hz, alpha$_2$ 9.75–12.5 Hz, beta$_1$ 12.75–18.5 Hz and beta$_2$ 18.75–35.0 Hz. To correlate the EEG changes with plasma concentrations, the values of the central lead of the dominant hemisphere (C_3) were used from the 17 channels derived. As the CATEEM system excludes the subdelta band (0.5–1.25 Hz) from the power spectral analysis, the raw EEG signal of this lead was transferred to a separate PC-based analysis tool. There, the power spectrum was analysed from 0.5 to 32 Hz and median frequency calculated subsequently (EEG-BASIC, version 2.4, Bonn, Germany), thus receiving more information during the pronounced hypnotic effect. Median frequency was used as a pharmacodynamic effect measure for modelling purposes.

Pharmacokinetic–pharmacodynamic modelling

Visual inspection of individual plasma concentration–median EEG frequency curves showed that the relationship could most adequately be described by a sigmoid Emax model[15]:

$$\mathrm{E}=\mathrm{E}_0-\frac{\mathrm{Emax}\times C_P{}^{\gamma}}{\mathrm{EC}_{50}{}^{\gamma}+C_P{}^{\gamma}}$$

where E=median frequency (Hz); E_0=baseline median frequency (Hz); Emax=maximum possible effect on median frequency attributable to the drug (Hz); C_P=plasma concentration of Ro 48-6791 (μg litre^{-1}); EC_{50}=plasma concentration of Ro 48-6791 (μg litre^{-1}) that gives 50% of the maximum attainable inhibition in median frequency; and γ=Hill coefficient, a variable which describes the steepness of the concentration–response relationship (no dimension).

Pharmacokinetic–pharmacodynamic modelling procedures were performed by incorporating a hypothetical effect compartment. The rate of drug transfer out of the effect compartment was characterized by the rate constant k_{eq} (h^{-1}). The half-life of equilibration ($T_{1/2eq}$) was calculated by ln $2/k_{eq}$. The pharmacodynamic model variables were estimated for the first infusion cycle by non-linear regression analysis using NONMEM and the optimum-fit pharmacokinetic variables.

STATISTICAL ANALYSIS

Differences between young and elderly volunteers were tested for statistical significance by the unpaired Student's *t* test. $P<0.05$ was considered statistically significant.

Results

SAFETY AND TOLERABILITY

All 18 subjects completed the study according to the design, without any serious adverse events. Apart from central depressant activity, few adverse events were reported. One young subject reported a fever lasting for approximately 15 h, 1 day after treatment with Ro 48-6791. Mild atrial arrhythmia and excessive dreaming, for 5 min during the second infusion cycle and during the night after drug administration, respectively, were reported by two elderly subjects. In a few subjects oxygen saturation decreased to less than the threshold set, but normalized immediately after administration of oxygen by mask. All participants breathed spontaneously during the entire observation period. Systolic, diastolic and mean arterial pressures, and heart rate, remained stable during the study in all subjects. Body temperature transiently decreased slightly to less than 35 °C in two elderly subjects. There was no pattern of abnormal laboratory values during the study which suggested a treatment effect, and the abnormalities observed were judged to be clinically irrelevant. The investigations performed at the post-study screen did not reveal clinically relevant differences from the baseline situation.

PHARMACOKINETICS

Table 1 presents the duration of each infusion cycle, time interval between the two cycles and dose of Ro 48-6791 administered in each cycle. Figure 2 shows the plasma concentration–time courses of Ro 48-6791 and Ro 48-6792 in a representative elderly subject. The fitted curves, on the basis of a three-compartment model for Ro 48-6791 and a two-compartment model for Ro 48-6792, are also given. In the ascending part of the two infusion cycles the concentration of the parent drug increased linearly with time. After the predetermined pharmacodynamic end-point had been reached, relatively constant concentrations of Ro 48-6791 were maintained for 15 min in most subjects. The metabolite Ro 48-6792 appeared rapidly in plasma and surpassed concentrations of the parent drug shortly after termination of the first infusion.

Table 1 Dose and duration of infusion of Ro 48-6791 in the two infusion cycles (mean (SD))

	Young	Elderly
Period A–B		
Duration (min)	42 (3)	43 (5)
Dose (mg)	15.4 (2.6)	8.4 (1.8)
Period C–D		
Duration (min)	34 (3)	38 (3)
Dose (mg)	11.0 (1.7)	6.9 (1.2)
Interval between cycles (min)	45 (10)	48 (11)
Total dose (mg)	26.4 (3.2)	15.2 (1.9)

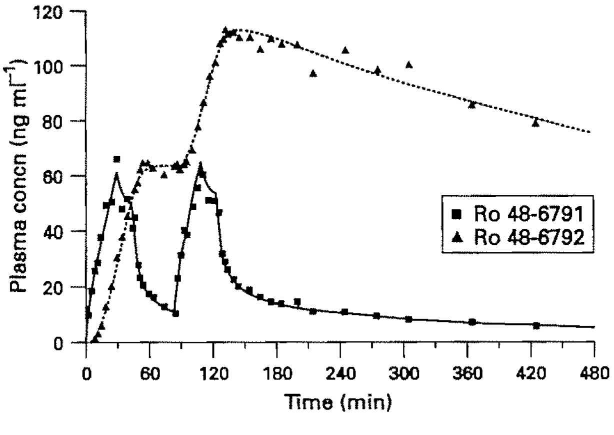

Figure 2 Actual and fitted plasma concentration–time course of Ro 48-6791 and Ro 48-6792 during and after both infusion cycles in a representative elderly subject (No. 101).

Table 2 Pharmacokinetic variables of Ro 48-6791 in young and elderly subjects analysed by an open three-compartment model (mean (SD))

	Young	Elderly
k_{12} (h^{-1})	11 (7)	7 (3)
k_{21} (h^{-1})	3.3 (1.3)	3.1 (0.9)
k_{13} (h^{-1})	3.3 (2.3)	3.8 (2.0)
k_{31} (h^{-1})	0.4 (0.3)	0.4 (0.1)
Cl_1 (litre h^{-1})	85 (23)	71 (15)
Cl_2 (litre h^{-1})	189 (47)	131 (33)
Cl_3 (litre h^{-1})	56 (22)	67 (29)
V_1 (litre)	20.5 (7.1)	19.5 (5.8)
V_2 (litre)	60.7 (14.8)	43.8 (13.0)
V_3 (litre)	152 (74)	162 (62)
V_{ss} (litre)	233 (80)	226 (57)
$T_{1/2}{}^{\alpha}$ (h)	0.041 (0.019)	0.046 (0.016)
$T_{1/2}{}^{\beta}$ (h)	0.56 (0.19)	0.49 (0.19)
$T_{1/2}{}^{\gamma}$ (h)	3.8 (1.4)	3.7 (0.8)

During the second infusion cycle, plasma concentrations of Ro 48-6792 accumulated further and by the end of the second infusion were much higher than those of Ro 48-6791. Thereafter, concentrations of Ro 48-6792 declined slowly in comparison with those of Ro 48-6791. In both groups, Ro 48-6791 showed a high plasma clearance, small initial volume of distribution and relatively short half-life (table 2).

PHARMACODYNAMICS

The time course of the changes in median EEG frequency during and after infusion of Ro 48-6791 in an elderly subject are shown in figure 3. Baseline median EEG frequency was approximately 7–9 Hz in all subjects. After the start of the first infusion, approximately 12 subjects initially showed a slight increase in median frequency. Relatively shortly before the pharmacodynamic end-point was reached, the effect variable decreased sharply to values close to 2 Hz. The time course of the return to baseline values in both recovery periods was steep. It

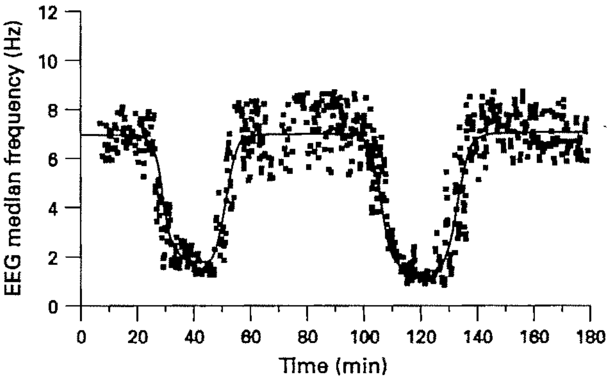

Figure 3 Median EEG frequency as a function of time during and after both infusion cycles in an elderly subject (No. 101).

appeared that during the second infusion cycle similar maximum drug effects occurred. Table 3 presents the pharmacodynamic variables estimated by fitting a sigmoid Emax function to the concentration–effect data of the first infusion cycle. Baseline values were slightly lower in the elderly than in the young subjects. Based on its EC_{50} values, Ro 48-6791 appeared to be a very potent benzodiazepine. Elderly subjects were more sensitive to the drug than young subjects. The concentration–effect relationship appeared to be steep, particularly in elderly subjects. Hysteresis between arterial plasma concentration and response was found in seven young and eight elderly subjects. Median k_{eq} values were similar in both groups. The equilibration half-life ($T_{1/2eq}$) was approximately 5–7 min. A representative plasma concentration–response plot during the first infusion cycle is given in figure 4 showing the hysteresis loop. Collapse of the hysteresis loop by incorporation of an effect compartment into the pharmacokinetic–pharmacodynamic model yields the effect compartment concentration–response plot of figure 5. In most subjects, the pharmacodynamic variable estimates of the first infusion cycle when applied to the second cycle led to less optimal characterization of the time course of effect in the latter (fig. 6).

Table 3 Pharmacodynamic variables of Ro 48-6791 in young and elderly subjects on the basis of a sigmoid Emax model and a hypothetical effect compartment. Values are means (SD) [median] of $n=9$. *$P<0.05$ compared with young subjects

	Young	Elderly
E_0 (Hz)	8.6 (2.4) [8.5]	7.4 (2.2) [7.0]
Emax (Hz)	7.0 (1.9) [6.9]	5.4 (1.3) [5.9]
EC_{50} (μg litre^{-1})	72 (25) [79]	44 (15) [42]*
γ	11 (7) [14]	34 (19) [45]
k_{eq} (h^{-1})	10 (6) [8]	14 (22) [6]

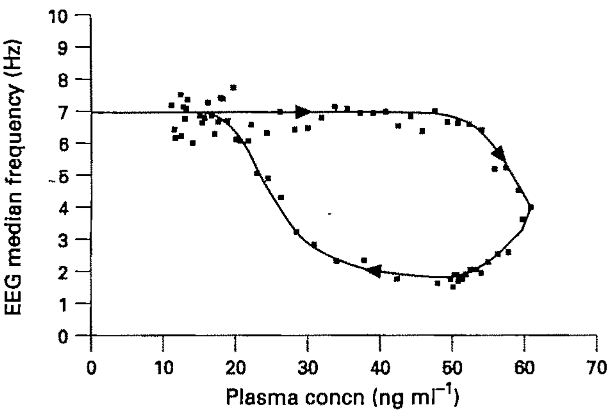

Figure 4 Relationship between arterial plasma concentration and median EEG frequency during the first infusion cycle in elderly subject No. 101.

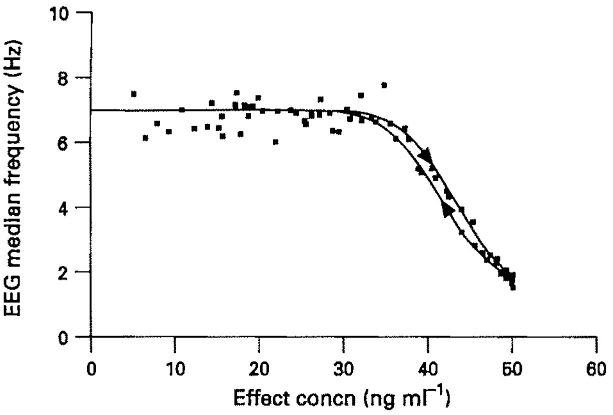

Figure 5 Relationship between drug concentration in the effect compartment and median EEG frequency during the first infusion cycle in elderly subject No. 101.

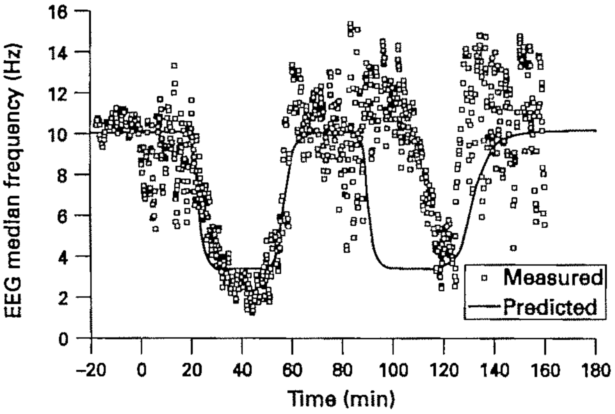

Figure 6 Median EEG frequency as a function of time during and after both infusion cycles in a young subject showing the poor fit of the data during the second infusion cycle.

Discussion

This is the second study in humans of the new benzodiazepine Ro 48-6791 which was developed to induce conscious sedation and anaesthesia, with or without other agents.[3]

Ro 48-6791 showed a favourable tolerability profile in both young and elderly subjects. There were only minor changes in cardiovascular and respiratory variables. Previous studies have shown that in this respect differences between various benzodiazepines are minor, even between long- and short-acting compounds.[16] It should be realized that in our study, high concentrations of Ro 48-6791 were attained at the pharmacodynamic end-point comparable with approximately 1200 μg litre^{-1} of midazolam. These concentrations are anticipated to be higher than those expected during therapeutic administration of Ro 48-6791. Anaesthetic conditions are seldom created by administration of a benzodiazepine alone. Monotreatment with Ro 48-6791 was used in this study to obtain information on tolerance, pharmacokinetics and pharmacodynamics. Obviously, Ro 48-6791 should still be studied in patients with compromised ventilatory function but this study did not provide indications that its profile would differ from that of midazolam.

The pharmacokinetics of Ro 48-6791 were described most accurately by an open three-compartment model. In this study the pharmacokinetics were examined by high-resolution techniques, involving frequent arterial blood sampling. This enabled accurate delineation of the distribution and elimination phases. In both groups clearance was markedly higher than that of midazolam.[17] In elderly subjects clearance was only approximately 15% lower than in young subjects, whereas the distribution rate constant from the central to the shallow peripheral compartment (k_{12}) decreased by one-third. Little change in pharmacokinetics with age has also been reported with midazolam.[18 19] Both Ro 48-6791 and midazolam are metabolized oxidatively by isoenzymes of cytochrome P450. However, clearance of Ro 48-6791 is high and, therefore, more dependent on liver blood flow than on the oxidative capacity of the liver. The ratio of volume of distribution *vs* compartmental clearance with respect to the deep peripheral compartment (V_3/Cl_3) correlates inversely with the context-sensitive half-time after drug infusions that have not yet reached steady-state conditions.[20] The context-sensitive half-time is the time needed for a 50% reduction in drug concentration at the active site. This is because drug is still being taken up into the deep compartment thereby contributing to a reduction in concentration in plasma and the effect compartment. In contrast, a small Cl_3/Cl_1 ratio correlates with a shorter context-sensitive half-time after an infusion to steady state. This particularly reflects how rapidly drug leaves the deep compartment. With Ro 48-6791, V_3/Cl_3 and Cl_3/Cl_1 ratios were, on average, 17% larger and 40% smaller, respectively, than those for midazolam. A 30% faster recovery is usually considered as a change that is clinically discernible given the underlying variation in both pharmacokinetics and pharmacodynamics in a given patient.[20] These ratios indicate that, based on the pharmacokinetics of Ro 48-6791 *per se*, this drug might demonstrate a shorter duration of action than midazolam. The concentration–time courses in all subjects showed linearly ascending plasma concentrations during both infusion cycles providing evidence that the computer which controlled the infusion pump was programmed correctly, be it with two-compartment pharmacokinetic data. This study confirmed that Ro 48-6792 had a markedly longer elimination half-life than the parent compound. The sampling schedule did not allow accurate estimation of its half-life.

The pharmacodynamics of Ro 48-6791 were investigated using median EEG frequency as the effect measure. In contrast with drugs such as barbiturates and etomidate, infusion of benzodiazepines does not induce burst suppression. Therefore, a different pharmacodynamic end-point was chosen in this study. The EEG variable total number of waves between 12 and 30 Hz derived by aperiodic analysis has been used for pharmacokinetic–pharmacodynamic modelling studies with midazolam.[21] Bührer and colleagues derived the variable microvolts per second also from aperiodic analysis in the 0.5–30 Hz band.[22] Other authors have used the change in power determined by fast Fourier transform in the 12–30 Hz frequency band to investigate the pharmacodynamics of benzodiazepines.[23] Alternatively, the percentage change in alpha band activity (7.5–13.4 Hz) has also been used.[24] The difficulties inherent in the selection of a single univariate EEG variable to quantify the effects of benzodiazepines were illustrated by Fiset and colleagues[25] who used both aperiodic analysis and fast Fourier transform to describe the EEG effects of midazolam in a study in 10 subjects. In our study median EEG frequency was used as the effect measure as it is more reflective of the total effects of Ro 48-6791 on the EEG. Moreover, this variable has been used successfully in pharmacokinetic–pharmacodynamic modelling investigations with thiopentone, etomidate, propofol and eltanolone[26–28] and, therefore, has found wider use than variables based on aperiodic analysis. Median EEG frequency fulfilled virtually all prerequisites for an effect measure in kinetic–dynamic investigations.[29] Its clinical relevance needs to be demonstrated in studies which integrate several clinical end-points.

This study revealed a high potency for Ro 48-6791. The variability in EC_{50} was pronounced. This phenomenon has been described repeatedly for the pharmacodynamics of benzodiazepines.[6] Coefficients of variation of up to 50% have been reported by other research groups.[21 25 30] EC_{50} values in the range 180–384 μg litre^{-1} have been estimated for i.v. midazolam.[21 22 25] Mandema and colleagues reported a mean EC_{50} of only 77 μg litre^{-1}.[30] This illustrates on the one hand the marked variability in the pharmacodynamics of benzodiazepines or applied methodology, or both, and on the other hand the need to compare drugs or subject groups, or both, with the same strictly standardized method.[31] However, we can conclude that Ro 48-6791 is more potent than midazolam, in line with the findings of the first study in humans.[7] The potency of Ro 48-6791 was approximately 40% higher in elderly compared with young subjects. Increasing sensitivity of the central nervous system with age is often reported.[32] However, controlled clinical studies which take into account both pharmacokinetics and pharmacodynamics as sources of variations in drug response are rare. Greenblatt and colleagues described a linear concentration–effect relationship for triazolam in young and elderly individuals with no difference in intrinsic sensitivity between the two groups.[33] Another study reported increasing pharmacodynamic sensitivity to the hypnotic effects of midazolam in elderly subjects.[34] It is interesting to note that the influence of age on sensitivity appears to be more pronounced with inhalation anaesthetics than benzodiazepines.[35]

The difference in EC_{50} between young and elderly subjects in combination with the reduced clearance in elderly explain to a large extent the difference in total dose given to both groups to elicit the same pharmacodynamic end-point. Hysteresis in the plasma concentration–effect relationship was detected in most subjects. Median k_{eq} values in both groups were similar (8 and 6 h^{-1}). This implies a half-time of equilibration between plasma drug concentration and effect ($T_{1/2eq}$) of approximately 6 min. Values of 2–3 min have been reported in studies on midazolam with arterial blood sampling.[21 22] However, the EEG methodology in our study was different and, therefore, direct comparison between the two drugs is necessary. The established concentration–response relationships were steep, as reflected in the variable γ. In particular, the values obtained in elderly subjects were high. It remains to be investigated if midazolam shows the same phenomenon.

The pharmacodynamic variables estimated on the basis of the concentration–response data of the first infusion cycle poorly predicted the time course of effect during the second cycle. The second infusion appeared to induce the same decrease in median frequency but with a delayed onset. No major change was found in offset. There may be several explanations for this phenomenon. First, the influence of the metabolite Ro 48-6792 cannot be excluded. The more rapid cessation of drug effect would then suggest inverse agonistic activity of Ro 48-6792. However, various animal experiments investigating mixtures of Ro 48-6791 and Ro 48-6792 in different dose ratios did not provide support for this hypothesis (Jenck, personal communication, 1995). The first clinical study did not suggest pharmacodynamic effects of Ro 48-6792 but maximum plasma concentrations reached were only approximately 25 μg $litre^{-1}$. Alternatively, acute tolerance may develop to the high-dose EEG effects of Ro 48-6791 in the course of this study. The development of tolerance to benzodiazepines has been studied by Breimer[36] and Kroboth and Smith[37] who concluded that acute tolerance may occur. Other investigators did not obtain data indicative of acute tolerance development.[25 38]

Acknowledgements

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British Journal of Anaesthesia 1997; **79**: 575–580

Pharmacokinetics of midazolam given as an intranasal spray to adult surgical patients

S. BJÖRKMAN, G. RIGEMAR AND J. IDVALL

Summary

The aim of this study was to determine the bioavailability and absorption kinetics of midazolam given as an intranasal (i.n.) spray. In addition, plasma concentrations of the active metabolite, 1-hydroxymidazolam, were measured to give an indication of enteral absorption. An i.v. and i.n. midazolam dose were given in a crossover study to 14 adult surgical patients. Individual uptake profiles of i.n. midazolam were estimated by numerical deconvolution. After an i.n. dose of 0.15 mg kg^{-1}, maximum arterial plasma concentrations were 192 (SD 48) μg $litre^{-1}$ at 14 (2) min. Uptake of midazolam was rapid and bioavailability was 83 (15) %. Formation of the 1-hydroxy metabolite after i.n. administration did not exceed that after the i.v. dose. This demonstrates that under optimal conditions absorption of midazolam via the nasal mucosa was virtually complete. In this case little midazolam was swallowed and subjected to first-pass metabolism in the liver and therefore pharmacologically important amounts of active metabolite were not produced. Routinely administering i.n. midazolam under the assumption that the bioavailability is approximately 50% (as reported previously in the literature) may lead to overdosing in some patients. (*Br. J. Anaesth.* 1997; **79**: 575–580).

Key words
Hypnotics benzodiazepine, midazolam. Pharmacokinetics, midazolam.

Midazolam given by the intranasal (i.n.) route provides a more rapid onset of effect than that after oral or rectal administration.[1–3] Plasma concentrations of midazolam have been studied after i.n. administration to children.[2–6] Mean bioavailability was estimated at 55% when plasma concentrations after i.n. or i.v. administration were compared in two separate groups of six children each.[5]

I.n. midazolam has also been used in adult patients to produce anxiolysis and sedation. The technique has been described for endoscopic procedures and dental treatment,[7–9] and it might be particularly convenient for mentally retarded patients frightened of medical interventions such as venous cannulation.[10]

Absorption through the nasal mucosa circumvents first-pass metabolism in the liver. If a mean bioavailability of 55% is found, what is the fate of the remaining 45%? In the cited studies,[1–10] midazolam was administered as drops of aqueous solution which, unless expelled through the nostrils, are eventually swallowed. Some midazolam could therefore have been absorbed from the gastrointestinal tract. The mean bioavailability of oral midazolam in children has been estimated at 15–27%, depending on the dose.[11] This low bioavailability is chiefly the result of extensive first-pass metabolism producing 1-hydroxymidazolam as the main metabolite.[12–14] This metabolite is almost equipotent with midazolam as a CNS depressant.[14 15] Thus even if the mean bioavailability of unchanged midazolam after i.n. administration is only 55%, formation of active metabolite after intestinal absorption of the remaining dose could theoretically result in a total pharmacological effect approaching that after parenteral administration. Plasma concentrations of 1-hydroxymidazolam after i.n. administration of midazolam have not been measured.

The aim of this study was to determine the bioavailability of midazolam given as an i.n. spray. A complete crossover design allowing separate determination in each subject was possible in 14 adult surgical patients.

Patients and methods

After approval by the regional Ethics Committee and the Swedish Medical Products Agency, and after obtaining informed consent, we studied 14 patients (seven females and seven males), ASA I–II, undergoing elective breast or throat surgery. Mean age was 43 (range 28–55) yr, weight 79 (SD 12) kg and height 174 (10) cm. Patients receiving drugs with known metabolic interactions with midazolam and those with any liver dysfunction were excluded, as were patients with rhinitis or nasal obstruction.

All patients were premedicated orally with dixyrazine 25 mg. After an initial dose of fentanyl 0.1 mg, anaesthesia was induced with midazolam

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SVEN BJÖRKMAN, PHD, Hospital Pharmacy, Malmo University Hospital, Malmo, Sweden. GUNILLA RIGEMAR, RN, JAN IDVALL, MD, PHD, Department of Anaesthesia, Västervik Hospital, S-593 81 Västervik, Sweden. Accepted for publication: June 14, 1997.
Correspondence to J. I.

0.15 mg/kg body weight given as an i.v. infusion of a 1 mg ml^{-1} solution (Dormicum, Roche AB, Sweden) over 2 min. Anaesthesia was maintained with intermittent i.v. injections of fentanyl (total dose during surgery 0–0.15 mg), and inhalation of isoflurane (end-tidal concentration 0.54–1.1%) and 70% nitrous oxide in oxygen. Neuromuscular block was produced with vecuronium and antagonized at the end of surgery with glycopyrronium–neostigmine. Mean duration of anaesthesia was 1.4 (range 0.8–3.0) h and of surgery 1.0 (range 0.6–2.5) h. In the recovery ward, where all patients stayed for 24 h, morphine was given for pain relief. In the evening, patients were given i.n. midazolam 0.15 mg/kg body weight. The drug was administered as a standard injectable solution (Dormicum) of 5 mg ml^{-1} with a spray bottle, with repeated sprayings alternating between nostrils. The spray bottle delivered a fine aerosol and the mean volume per activation was 0.09 (range 0.07–0.11) ml.

Monitoring during surgery and in the recovery ward included indirect arterial pressure, heart rate and arterial oxygen saturation (Sp_{O_2}) by pulse oximetry. Blood samples for drug assays were obtained from an arterial cannula inserted before induction of anaesthesia and kept patent with the aid of a continuous saline infusion (3 ml h^{-1}). Sampling was performed before and at 2, 4, 6, 9, 12, 15, 20 and 30 min and 1, 1.5, 2, 3, 4, 6, 8 and 10 h after the start of the i.v. infusion. Another sample was obtained before i.n. administration, 2–3.8 h later. Blood sampling was at 2, 4, 6, 9, 12, 15, 20, 30 min and 1, 1.5, 2, 3, 4, 6, 8 and 10 h. In the first five patients, blood sampling started after completion of spraying. As this was found to take several minutes, sampling in the remaining patients was scheduled from the beginning of administration and time to completion was noted. Consequently, the total time of each study was 22–24 h, and any deviation from the scheduled sampling time was noted and the true time used in data processing. Total blood sampling volume was 260 ml. Mean peroperative blood loss was 160 (range 25–350) ml.

Blood samples were kept on ice for a maximum of 2 h until centrifuged. Plasma was stored at −20 °C until assay within 8–12 weeks. The syringes and spray bottles were weighed before and after administration of their contents, and samples of the solutions were saved for assay.

Plasma samples were assayed for midazolam by gas–liquid chromatography (GLC) with electron capture detection[16 17] after addition of diazepam as internal standard and extraction with diethyl ether. The within-day coefficient of variation (cv) was 4.6% at 7.5 μg $litre^{-1}$ (3 ng $sample^{-1}$), 3.0% at 75 μg $litre^{-1}$ and 3.1% at 750 μg $litre^{-1}$ ($n=8$). The limit of detection was approximately 1 μg $litre^{-1}$, and the between-day cv was 11% at 60 μg $litre^{-1}$ ($n=8$). For each patient, samples from i.v. and i.n. administrations were assayed on the same day.

Plasma samples from eight patients were also assayed for 1-hydroxymidazolam by high pressure liquid chromatography (HPLC).[18] The within-day cv was 11% at 4 μg $litre^{-1}$ and 3.1% at 10 μg $litre^{-1}$, and the limit of detection was approximately 2 μg $litre^{-1}$.

Concentrations of midazolam in the i.v. and i.n. solutions were determined by HPLC[18] using the same standards as for the plasma assay, and each actual dose was calculated from the weight of administered solution and its measured concentration of midazolam.[19] Conventional compartmental models with elimination from the central compartment were fitted to the plasma concentration data from the i.v. administration, using PCNONLIN software (Scientific Consulting Inc., Apex, NC, USA). The final choice of model and weighting was three compartments and $concentration^{-1}$. The set of variables obtained included clearance (Cl), volume of distribution at steady state (V^{ss}), mean residence time (MRT) and terminal half-life ($T_{1/2}{}^{\gamma}$).

The contribution from the i.v. injection to the plasma concentration of midazolam after i.n. administration was subtracted from all measured concentrations, as shown in figure 1. The area under the concentration curves after i.v. and i.n. administration ($AUC_{i.v.}$ and $AUC_{i.n.}$) were calculated by the logarithmic trapezoidal method.[20] In both cases, extrapolation to infinite time was based on the terminal hybrid rate constant obtained from the PCNONLIN fit to the i.v. data. The bioavailability based on the AUC (F_{AUC}) of i.n. midazolam was then calculated using the standard formula:

$$F_{AUC}=\frac{AUC_{i.n.}\times dose_{i.v.}}{AUC_{i.v.}\times dose_{i.n.}} \qquad (1)$$

The absorption profile of i.n. midazolam was estimated by numerical deconvolution (fig. 2).[21] The PCNONLIN fit provided the theoretical disposition function of midazolam after instantaneous injection (as opposed to actual 2-min infusions), calculated by analytical deconvolution.[22] This equation was divided by the dose (in μg) to give the unit disposition function (UDF), that is the triexponential function that would describe the plasma concentration curve of midazolam after instantaneous injection of one dose unit (here, 1 μg). Numerical deconvolution

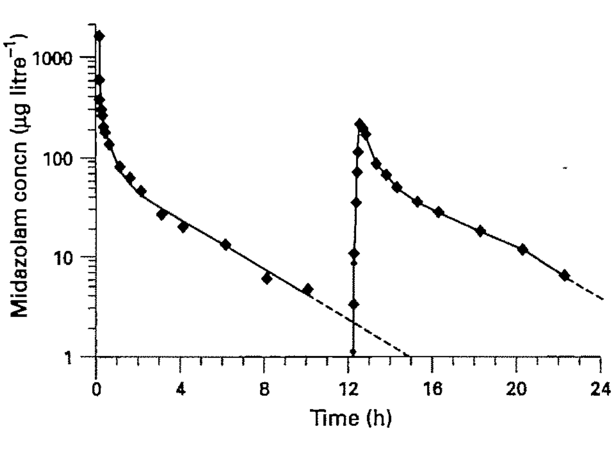

Figure 1 Arterial plasma concentration curves of midazolam in one patient during the study. A three-compartment model was fitted to the 0–10 h data after i.v. infusion. The symbols on the concentration curve after i.n. administration are concentrations after subtraction of the contribution from the i.v. infusion (in this case 1.9% of the total AUC after i.n. administration). After the first three data points, this difference is no longer visible. Broken lines=extrapolations based on the three-compartment fit. The extrapolated fraction of the AUC after i.n. administration was 5.9%.

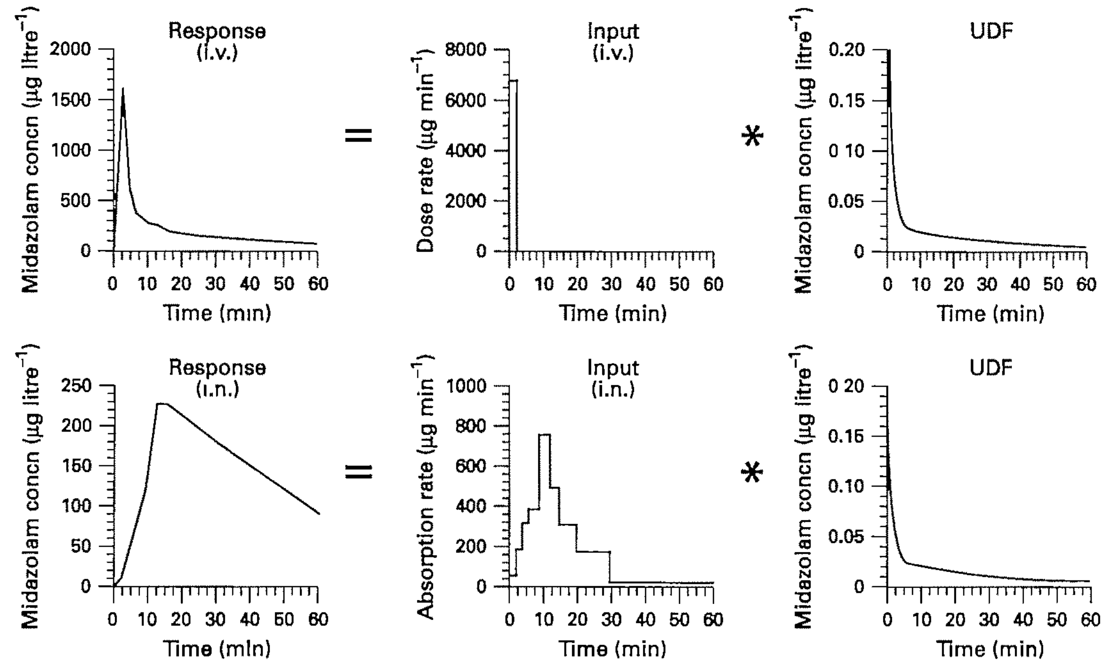

Figure 2 The principle of the deconvolution procedure. The asterisk denotes combination of two functions (curves) by the mathematical process of convolution. Top: observed pharmacokinetic response (i.e. plasma concentration curve) results from the input function of the drug (i.e. rate and duration of infusion) and the unit disposition function (UDF, i.e. the pharmacokinetics of the drug after instantaneous introduction of one dose unit, here 1 µg, into the circulation). The response is measured, the input is known and UDF can be calculated by deconvolution. Bottom: response (i.e. plasma concentration curve) is different from above as the input function has changed from a 2-min infusion to absorption with variable rate. As the response is measured and the UDF is known (and assumed to be unchanged) from the i.v. experiment, the input function can be estimated by deconvolution. Data are from the same patient as in figure 1.

of the i.n. plasma concentration curve and the UDF yielded the input function, which is the absorption profile of the drug. The input function was computationally constrained to be positive. The software was provided by Dr Davide Verotta, University of California at San Francisco, USA.

Integration of the input function gives the total absorbed amount of midazolam as a function of time. Bioavailability based on input (F_{inp}) was therefore calculated as:

$$F_{\text{inp}} = \frac{I_{\text{cum}}}{\text{dose}_{\text{i.n}}} \qquad (2)$$

where I_{cum}=cumulated input, that is absorbed midazolam at 10 h after dosing. This gives a cross-validation of the results.

The Student's *t* test was used to evaluate the statistical significance of the differences between the bioavailability of midazolam and 100% (unpaired test) and of drug-induced changes in arterial pressure (paired test). The level of significance was set at $P<0.05$ in one-tailed tests.

Results

The plasma concentration curves of midazolam for all patients are shown in figure 3 and the main pharmacokinetic variables in table 1. The absorption profiles of midazolam after i.n. administration are shown in figure 4. Bioavailability was generally high, with an excellent correlation (r^2=0.965) between F_{AUC} and F_{inp}. Mean values of F_{AUC} and F_{inp} were, however, both significantly different from 100%.

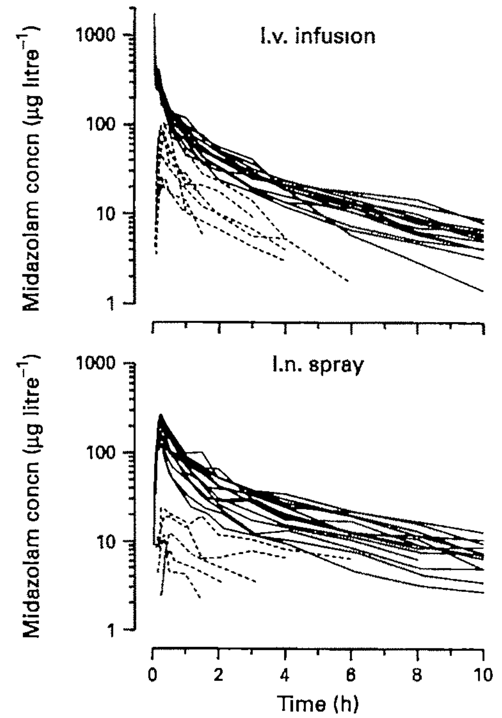

Figure 3 Individual arterial plasma concentration curves of midazolam (continuous) in 14 patients after i.v. and i.n. administration. Contributions from the i.v. infusion to the plasma concentrations after i.n. administration have been subtracted. These ranged from 0.3 to 6.3 µg litre^{-1} at 0 min and from <0.05 to 1.6 µg litre^{-1} at the end. The metabolite, 1-hydroxymidazolam (broken curves) was assayed in eight patients but was not detected reliably after i.n. administration in three.

Table 1 Main pharmacokinetic variables of midazolam after i.v. and i.n. administration to 14 surgical patients. The estimated tC_pmax is after the start of i.n. administration. Patient No. 4 was an outlier with a poorly estimated $T_{1/2}{}^{\gamma}$, and the values in parentheses are not included in mean (SD). For patient Nos 6–14, F_{AUC} was 87 (15) %

		After i.v. infusion				After i.n. administration			
Patient No.	Weight (kg)	*Cl* (litre min^{-1})	V^{ss} (litre)	MRT (min)	$t_{1/2}{}^{\gamma}$ (min)	$C_p$max (μg litre^{-1})	tC_pmax (min)	F_{AUC} (%)	F_{mp} (%)
1	56	0.48	72	149	155	125	14	67	nd
2	82	0.43	89	205	227	209	16	93	nd
3	79	0.63	104	166	165	168	10	68	nd
4	58	(0.45)	(209)	(462)	(943)	143	12	(59)	nd
5	93	0.55	89	163	185	179	16	69	nd
6	79	0.51	81	159	205	253	14	74	75
7	88	0.61	88	143	143	159	14	93	92
8	86	0.49	113	232	260	198	15	67	66
9	96	0.54	73	136	146	227	14	86	85
10	84	0.62	80	129	182	124	15	85	80
11	70	0.44	71	160	165	216	15	99	98
12	74	0.56	59	105	83	253	12	108	115
13	78	0.42	50	121	129	162	15	67	69
14	82	0.43	63	147	149	267	15	103	108
Mean	79	0.514	79	155	169	192	14	83	88
SD	12	0.075	18	34	45	48	2	15	17

Uptake from the nasal mucosa was rapid and close to completion within 1–2 h (fig. 4). Dose-normalized AUC after i.n. administration varied 2.2-fold, from 1.13 to 2.47 min litre^{-1}, compared with 1.5-fold (1.62–2.41 min litre^{-1}) after i.v. infusion. The contribution from i.v. infusion to the total AUC after i.n. administration was 3.7 (2.7) %, and the error caused by subtraction would be a fraction of this percentage.

The concentration curves of 1-hydroxymidazolam in eight of the patients are included in figure 3. After i.v. infusion of midazolam, the $C_p$max of the metabolite was 28–104 μg litre^{-1} at 12–20 min. After i.n. administration of midazolam, $C_p$max for 1-hydroxymidazolam ranged from undetectable to 24 μg litre^{-1} at 15–26 min after the beginning of administration.

The i.v. dose of midazolam induced hypnosis in all patients within 4 min. Cardiovascular variables were stable with an initial mean arterial pressure (MAP) of 105 (11) mm Hg and with a maximum reduction (ns) to 96 (10) mm Hg within 15 min of induction of

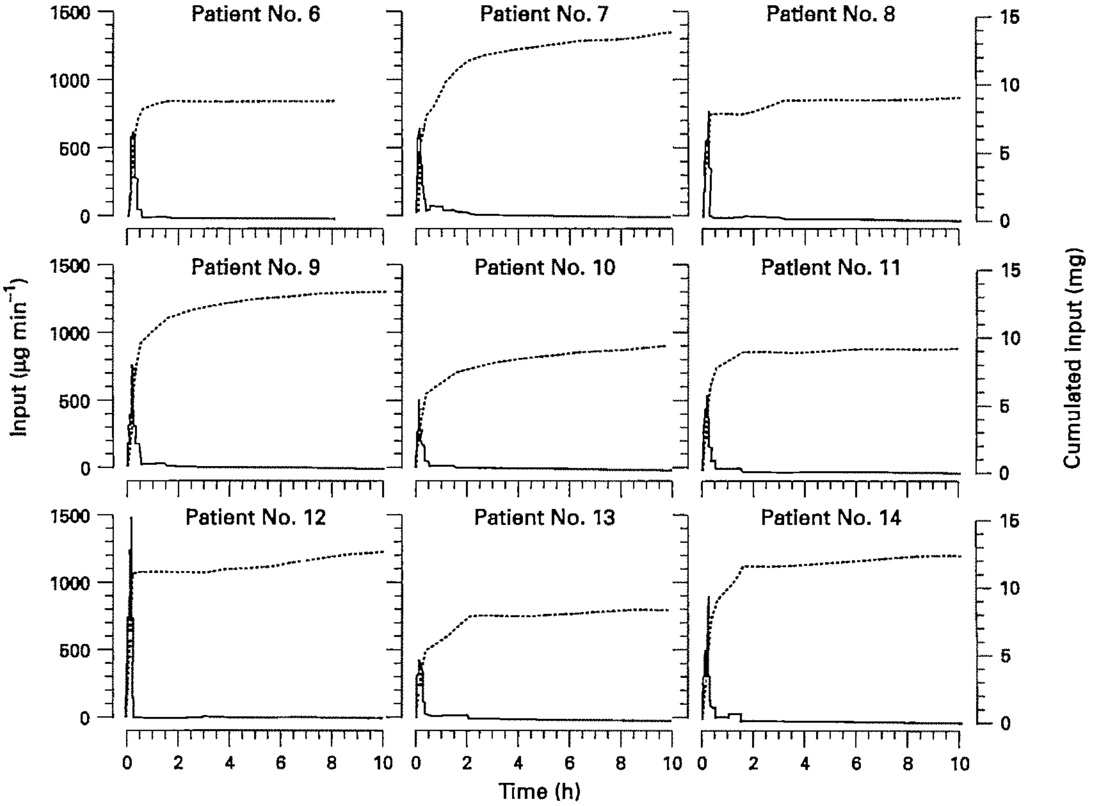

Figure 4 The input function, that is absorption of midazolam from the nasal mucosa (μg min^{-1}) during each blood sampling interval, and cumulated input (broken curve), that is total amount absorbed over time, in nine patients, with blood sampling from the beginning of i.n. administration. This took an average of 10 (range 8–13) min.

anaesthesia. The same dose administered i.n. had a less profound effect and a slower onset. After 6–14 min, that is a few minutes before mean tC_Pmax, all patients fell asleep but were rousable. Some patients found the solution slightly irritating or tickling, but all found the procedure acceptable. Cardiovascular variables were stable, MAP decreasing from 108 (12) to 105 (9) mm Hg (ns) when patients fell asleep. During anaesthesia Sp_{O_2} remained greater than 95% in all patients, but after i.n. midazolam administration desaturations occurred in five patients necessitating extra oxygen (5 litre min^{-1} by face mask) to achieve Sp_{O_2} >95%.

Discussion

This study had demonstrated that under optimal conditions absorption of midazolam via the nasal mucosa can be rapid and virtually complete. Routinely using an i.n. dose of midazolam that is twice the i.v. dose under the assumption that bioavailability is approximately 50% may lead to overdosing in some patients. The earlier study in childen[5] was not a crossover study and calculation of the rate of uptake of midazolam from the nasal mucosa was not attempted. In addition, administration of midazolam as i.n. drops may cause loss of solution either as sneezing,[1 3] spilling[4] or swallowing, all of which result in underestimation of bioavailability. As midazolam is not available in solutions higher than 5 mg ml^{-1}, large volumes must be given (at least 2 ml in normal adults).[7–10] Some of this solution is probably swallowed. We minimized spilling and swallowing by slow and careful spraying of approximately 0.1-ml aliquots. This proved time-consuming. However, in a 15-kg child three sprayings in each nostril would be sufficient to give a recommended[1 3] 0.2 mg kg^{-1} dose of midazolam.

The bioavailability of i.n. midazolam given by spray was greater than after oral administration in adults, with reported mean values in various groups of subjects of 46–68% (depending on dose),[12] 44%[23] or 36–50%.[24] As very little i.n. midazolam was apparently absorbed by the gastrointestinal route, the formation of 1-hydroxymidazolam did not exceed that after a parenteral dose of midazolam.

The deconvolution analysis revealed rapid uptake of midazolam, presumably chiefly from the nasal mucosa, in most patients. A more prolonged uptake, as in patient Nos 7, 10 and 13 (fig. 4), could to some extent be by gastrointestinal absorption. The tC_Pmax of midazolam was, however, highly reproducible at 14 (range 10–16) min after the beginning of spraying, and $C_P$max reasonably so at 192 (range 124–267) µg litre^{-1}. Similar mean tC_Pmax values of 13 min,[2] 10 min,[4] 12 min[5] or 12–16 min (with different doses)[6] were found after rapid instillation of i.n. midazolam solution in children. This suggests that absorption from the nasal mucosa is rate limiting and the time taken to administer the spray is relatively unimportant. Inter-individual variation in $C_P$max was similar[5] or tended to be greater[2 4 6] in the earlier studies compared with ours.

Midazolam was used as an i.v. induction agent before surgery and then as a hypnotic in the evening. Thus a crossover design was achieved with valid medical indications for both doses. This implied however that the i.v. dose was invariably given in the morning and the i.n. dose in the evening. As there is no apparent circadian variation in the clearance of midazolam,[25] we feel that this design was justified. We also avoided major (intra-abdominal) surgery which may influence the pharmacokinetics of midazolam.[26–28] Minor surgery[27] or administration of volatile anaesthetics[29] have not been found to significantly affect the disposition of midazolam. Putative interactions of anaesthesia, other medications and surgery would tend to lower clearance, that is increase the AUC_{iv} of midazolam. As the AUC_{iv} is in the denominator in equation (1), this would cause underestimation of F_{AUC} (and influence F_{inp} in a similar manner). The "true" F values would in this case be higher than we calculated.

The pharmacokinetic variables of midazolam after i.v. administration were also in good agreement with earlier findings in young to middle-aged healthy volunteers or patients undergoing minor surgery.[12 14 24 26 27 30–34] In studies using 12–24 h blood sampling, the mean terminal $T_{1/2}$ of midazolam was normally estimated at 2.1–3.3 h.[12 24 26 27 31–33] In approximately 6% of the population a considerably longer terminal $T_{1/2}$ was found,[27 33] and in our study this occurred in one of 14 subjects.

The observation that all patients were asleep but rousable a few minutes before a $C_P$max of 192 (48) µg litre^{-1} was reached is in good agreement with previous findings[30] at midazolam plasma concentrations of 150–200 µg litre^{-1}. In a later study in volunteers[34] a midazolam concentration of 131 (14) µg litre^{-1} at awakening was observed. In all studies, however, effects were recorded during non-steady state conditions, ignoring any effect of hysteresis[14] of midazolam. All patients had stable haemodynamic variables and minor oxygen desaturation was seen in only five patients, which is in good agreement with earlier findings on i.n. midazolam.[1 2 6 8 9]

In conclusion, this study has shown that the bioavailability of midazolam administered via the nasal mucosa was high and that active metabolite was not formed in pharmacologically important amounts. However, to achieve this, it is important to optimize nasal delivery by slow and careful spraying of the drug solution to avoid losses or swallowing. A good technique for doing this also in small children should be developed in order to fully exploit the advantageous pharmacokinetic and pharmacodynamic properties of midazolam.

Acknowledgements

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Magnetic resonance spectroscopy of isoflurane kinetics in humans. Part I: elimination from the head

G. G. LOCKWOOD, D. P. DOB, D. J. BRYANT, J. A. WILSON, J. SARGENTONI,
S. M. SAPSED-BYRNE, D. N. F. HARRIS AND D. K. MENON

Summary

We describe the first human experiments to demonstrate wash-out of isoflurane using fluorine magnetic resonance spectroscopy. Using a surface receive coil, we found two-compartment kinetics within the head with decay half-times of 9.5 and 130 min, but the signal was too weak to localize the compartments. If the fast compartment is assumed to be the brain then our results match the predictions of the classical perfusion-limited pharmacokinetic model of inhalation anaesthesia. (*Br. J. Anaesth.* 1997; **79**: 581–585).

Key words
Anaesthetics volatile, isoflurane. Pharmacokinetics, isoflurane. Measurement techniques, magnetic resonance spectroscopy.

In the classical pharmacokinetic theory of inhalation anaesthesia, an inhaled anaesthetic is considered as an inert gas, the partial pressure of which slowly equilibrates throughout the body.[1] The partial pressure in each tissue approaches arterial partial pressure exponentially with a rate constant proportional to the perfusion of that tissue and to the ratio of blood solubility to tissue solubility for that anaesthetic. Inter-tissue diffusion and specific tissue binding are not usually considered. Published values of brain perfusion[2 3] and isoflurane solubility[4] predict a half-time for the equilibration between arterial blood and brain of 2–3 min. There are no specific binding sites of quantitative significance in the brain,[5] and no evidence of chemical bonding to body tissues,[6 7] so wash-out kinetics should match wash-in. The overall elimination of isoflurane from the brain at the end of an anaesthetic is slower than this because the concentration in arterial blood declines gradually (clearance by the lungs is imperfect), and the longer the anaesthetic, the slower the elimination from the brain as a greater drug load must also be cleared from the remainder of the body. One model of this process[8] predicts an elimination half-time of 7 min after 30 min of anaesthesia.

Fluorine magnetic resonance spectroscopy (^{19}F MRS) allows pharmacokinetic investigation *in vivo* because all modern inhalation anaesthetics are fluorinated. The first animal MRS experiments with halothane demonstrated very slow elimination of halothane from the brain, incompatible with the classical model.[9] Some of that MRS signal probably arose from fluorinated metabolites, and there has been debate over the identity of the tissue source of the signal.[10 11] Later animal studies demonstrated fast and slow compartments within the head (usually assumed to be brain and extra-cerebral tissue, respectively), but even in recent studies of isoflurane, estimates of the faster half-time have been greater than predicted by theory (36 min,[12] 25 min[13]) with only one exception (8 min[14]). A persistent problem with these studies is that the ^{19}F signal is too weak to allow dynamic imaging, and the location of the signal source has been estimated indirectly.

The question of delayed cerebral elimination of anaesthetics has obvious implications both for the recovery of "street fitness" in patients after anaesthesia and the validity of the standard perfusion-limited model of anaesthetic distribution. We have investigated this problem by undertaking the first ^{19}F MRS studies of isoflurane kinetics in humans. In this part of the study we have examined elimination of isoflurane from the head; in part II[15] the data are re-examined to estimate the rate of equilibration between end-expired gas and brain.

Subjects and methods

We studied healthy volunteers, aged 30–41 yr. Subjects gave written informed consent and the study was approved by the Medical Research Ethics Committee of Hammersmith Hospital and the Royal Postgraduate Medical School. Subjects lay in the left lateral position in the bore of the spectrometer and breathed oxygen via a Mapleson A system incorporating a non-ferromagnetic valve venting outside the magnet bore to eliminate trace concentrations of isoflurane in the air around the subject's head. The nares were occluded and subjects breathed through a

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G. G. LOCKWOOD, MB, BS, FRCA, BSC, D. P. DOB, BSC, MB, BS, FRCA, J. A. WILSON, FRCA, S M. SAPSED-BYRNE, AIBIOL, BSC, D. N. F. HARRIS, MD, FRCA (Department of Anaesthesia), D. J. BRYANT, PHD, J. SARGENTONI, DCR(R) MU (Robert Steiner Magnetic Resonance Unit); Hammersmith Hospital, London W12 0HS. D. K. MENON, MB, BS, FRCA, MRCP, PHD, Department of Anaesthesia, Addenbrooke's Hospital, Cambridge Accepted for publication: June 13, 1997.

snorkel-style mouthpiece. There was no ^{19}F MR signal from the apparatus used. Pulse oximeter and ECG leads were passed through low pass filters to shield the spectrometer from radio frequency interference. End-tidal carbon dioxide and isoflurane concentrations were measured throughout using an infrared monitor (Capnomac, Datex, Finland) sampling via a catheter 6 m long. The monitor was calibrated before each experiment using QuickCal Standard (Datex, Finland). Digital output from the Capnomac was logged onto a computer and the analogue output of the volatile anaesthetic channel was recorded on paper. Subjects were attended by two anaesthetists: one remained outside the spectrometer's radio frequency screening enclosure watching the electronic monitors, the other was inside the enclosure monitoring respiration. Baseline measurements were made, and then a constant concentration of isoflurane (0.6% or 1%) was introduced into the inspired gas.

The spectrometer was a prototype Picker system operating at 1.5 T corresponding to a frequency of 64 MHz for fluorine and 60 MHz for protons. The transmitter coil was of saddle shape geometry, 52 cm in diameter, and could be tuned independently to both required operating frequencies. Radio frequency pulses of 200 ms could be generated for both ^{1}H and ^{19}F components of the study with this transmitter system and had sufficient bandwidth to excite equally all resonances of the ^{19}F spectrum. A 6 cm coil, also tuneable to both 64 and 60 MHz, was positioned over the subject's occipital region. This combination of coils gave a homogeneous transmit pulse over the whole head of the subject together with the improved sensitivity of a closely coupled receiver coil. The system was shimmed using the proton signal before acquisition of the ^{19}F spectra. The radio frequency pulse was calibrated by an external non-resonant search coil to monitor the transmit (B_1) field directly. This search coil had previously been calibrated using a concentrated ^{19}F phantom in place of the subject's head. The homogeneity provided by the use of a body transmitter coil ensured that this positioning was not critical.

Continuous data collections were made, each comprising 128 averages (256 for the initial study), with collection starting within 400 μs of the pulse and a repetition time of 1 s. During the sequence of experiments, presaturation sequences were designed which would eliminate the magnetic resonance signal from an operator-selectable plane. They were used in the last two experiments, interleaved with the standard sequences, in an attempt to eliminate the signal from the superficial tissues.

The MRS peak height data collected during the period of elimination were normalized to peak height before isoflurane was stopped and modelled by one, two and three exponential equations. The F test criterion advocated by Boxenbaum, Riegelman and Elashoff[16] was used to decide which model was supported best by the data. Conventionally, the significance of such curve fitting can be improved by pooling data from different subjects: the number of data points is increased but the number of variables to be fitted is unchanged. The coefficients and rate constants of the curve derived from the pooled data are then group coefficients and group rate constants. Unfortunately, our data were in arbitrary units which differed between subjects because the signal strength was so sensitive to the position of the surface coil, and there was no prospect of obtaining meaningful group coefficients. None the less, individual curve fitting can be undertaken simultaneously with the constraint that they all have the same rate constants (the group rate constants) with individual coefficients and group rate constants chosen to provide the best fit. The fit of single and biexponential equations to the pooled data can then be tested by the same F test criterion used for individual data sets. All curve fitting was performed by iteration using the Solver function of a Microsoft Excel v4 spreadsheet, with least squares solutions approximated from several initial variable values and checked visually to ensure that true minima had been found.

Results

A total of eight studies were undertaken on five volunteers (see table 1, fig. 1). Only five studies produced wash-out data. The other studies were terminated prematurely because the subject became restless before regaining consciousness. When this happened the subject was withdrawn immediately from the magnet bore and wash-out data were lost.

When each experiment was analysed individually, a biexponential equation was a significantly better fit to the data than a single exponential in only two experiments (table 1). However, when the data sets were pooled, there was strong overall support for biexponential decay ($P<0.00001$). No data set supported a three-exponential equation.

Presaturation pulses were used in two studies but

Table 1 Results of the studies undertaken in five volunteers

Subject No.	Concentration and duration of isoflurane	Wash-out data points	$T_{1/2}$, fast	$T_{1/2}$, slow	Signif. of 2 exponentials	Comments
1	0.25%, 10 min + 0.5%, 35 min	8	—	57	ns	Initial study. 5-min data acquisition
2	0.6%, 2 5min	17	4.7	92	0.002	2-min data acquisition for this and all following studies
3	1%, 30 min	30	5.9	74	0.00001	
4	1%, 30 min	12	—	25	ns	Presaturation pulses obliterated all signal
5	1%, 35 min	12	—	121	ns	Presaturation pulses obliterated all signal
Group		79	9.5	130	0.00001	The best fit when the model for each data set was constrained to share group half-times

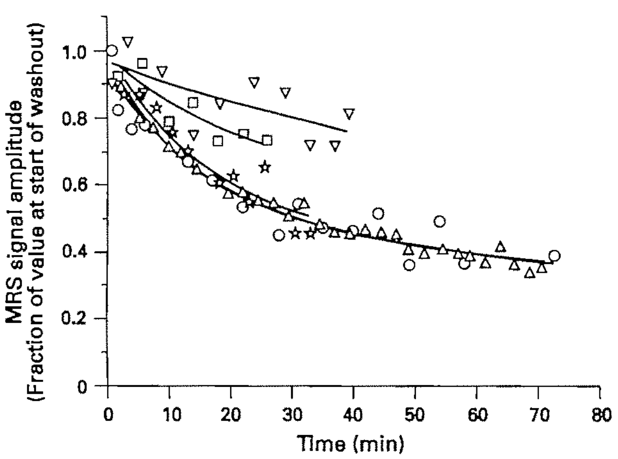

Figure 1 Wash-out of the ^{19}F MRS signal for each of the five subjects. Each subject's data are expressed as a fraction of the signal amplitude at the start of wash-out. Also shown are the biexponential curves of best fit, assuming all subjects shared the same fast and slow elimination half-times.

the signal was so diminished that peak heights could not be distinguished from noise.

Discussion

This study was undertaken because of inconsistencies in results from animal experiments and their deviation from the theoretical prediction of an elimination half-time of 5–10 min. In 1983, Wyrwicz and colleagues made the first *in vivo* observations of the kinetics of inhalation anaesthesia in rabbits using ^{19}F MRS.[9] They reported prolonged elimination of halothane from the brain with a half-time of several hours. These results were challenged by Strum, Johnson and Eger,[17] arguing from *in vitro* studies, but it was not until 1987 that further ^{19}F MRS studies appeared. Wyrwicz's group found biexponential elimination kinetics for halothane[18] and isoflurane[13] (the faster having a half-time of 25 min for both agents), but as both components were detected after surgical removal of extracranial tissues it was still concluded that there was a slow component to the elimination of anaesthetics from the rabbit brain with a half-time of 3–5 h. Litt and colleagues, using a different MRS technique to eliminate the signal from surface tissues, also found biexponential elimination kinetics of halothane from rat brain but the half-times were only 6 and 23 min.[19] The same group also studied the elimination of isoflurane from rabbit brain.[12] They found that elimination had a single component (half-time 36 min) when the skull was removed and a small surface coil applied directly to the brain, but two half-times of 55 min and 5 h in a single animal when a larger coil (matching that used by Wyrwicz and colleagues) was applied to the intact head. Their conclusion was that the long elimination half-time found by Wyrwicz and colleagues arose from tissue outside the brain, but their fast component results still disagreed with theory. They later compared the kinetics of halothane, isoflurane and desflurane in craniectomized rabbits, producing data compatible with perfusion-limited kinetics (half-times of approximately 8 and 60 min for all agents). Litt's group also produced images showing halothane exclusively in non-brain structures within the rabbit head,[20] although the MRS collection variables biased this study towards these areas. The opinions of these two groups remained unresolved, with each still vigorously defending their position in 1991,[10,11] but others were prepared to accept the fast component of halothane elimination from the rat head as an indicator of cerebral blood flow.[21]

Recently, Xu and co-workers found two-compartment kinetics for sevoflurane in the rat head with half-times of 14 and 100 min.[22] Sequential fluorine images showed initial accumulation of sevoflurane in brain, and one MRS characteristic of the two compartments (their T_2) provided further evidence that the fast compartment was the brain. Although the weight of evidence from animal work may now suggest that elimination of fluorinated anaesthetics from the brain is rapid, Wyrwicz and colleagues maintain that there is slow elimination from the brain, and the studies from Litt's group have not been consistent.[12,14] Even the results of Xu and colleagues, although technically impressive, give a half-time of sevoflurane elimination from the rat brain which is twice that expected from simple pharmacokinetic theory.

This is the first ^{19}F MRS study of the kinetics of inhalation agents in humans. Inhalation of isoflurane to the point of unconsciousness, and subsequent recovery, may be associated with restlessness, confusion and loss of airway control. It is therefore difficult to perform these experiments in the bore of a magnetic resonance spectrometer because the subject lies within a tunnel 6 ft long and 30 inches in diameter. Restlessness demands that the experiment be terminated so that the subject can be withdrawn from the magnet bore for safety, but any change in position of the subject's head relative to the receive coil invalidates further data collections. The studies therefore have some risk and a poor data yield. Nevertheless the investigation was pursued because human studies alone allow anaesthetic effects on consciousness to be related to tissue compartment concentrations: animal experiments are performed with background i.v. anaesthesia. This aspect of the study is reported in part II of the study.[15]

We have found evidence of biexponential wash-out of isoflurane from the head. The longer averaging used in the pilot study precluded the identification of a fast component of elimination, but the next two studies produced consistent data supporting two compartments. The improvement obtained by fitting a two- rather than a one-compartment model was not statistically significant in the last two subjects. This may be because fewer data points were collected from these experiments (the experiment was terminated when the subject became too restless), but there is another possible explanation. During this series of experiments the spectrometer was overhauled and modified, which included installation of electronic decoupling between receive and transmit coils (the previous decoupling was geometrical). An incidental result of the improved decoupling was to reduce the sensitivity of the surface coil to deeper tissues and if, as we believe, the fast component is deep, it would be more difficult to identify in the total signal. The timetable for hardware modifications to the spectrometer was unfortunately not under our control. In order to determine the overall significance of our evidence for biexponential elimination, we argued that regional perfusion of the head (which determines the kinetics of the underlying compartments) would be similar between subjects and that the more variable parameters would be the relative strength of the signal from the compartments because this depends critically on the exact position of the coil relative to the scalp, cranium and brain. We therefore re-computed the best fitting single and biexponential equations for all of our subjects simultaneously, subject to the constraint that all five shared the same half time(s). This analysis gave strong support for biexponential elimination.

The presaturation pulses were intended to resolve the two components spatially. Ideally the plane of the pulse obliterating the MR signal would have been so sharply defined that signal from adjacent areas was unaffected. Some encroachment into brain tissue was inevitable, but we thought that enough signal would remain to estimate isoflurane kinetics in purely brain tissue. In the two studies for which presaturation sequences were available there was no significant fast component and it is not surprising that almost all the signal was lost after presaturation of the superficial plane. This part of the study therefore only enables us to say that most of the signal is superficial, as is inevitable with a surface coil, and in particular we cannot refute the claim that there is a slow component in the deeper structures. None the less, the match of experimental and computer-generated results suggests that the fast compartment is brain and the slow is superficial tissue.

Our half-times were substantially shorter than those reported from most animal studies. This may be explained by species differences, but there were experimental differences which may also have contributed. Our subjects were exposed to isoflurane for relatively short durations; slow compartments would not have absorbed much isoflurane and their contribution to the MRS signal would be modest even though the ^{19}F signal from non-cerebral tissues decays more slowly and can be collected more efficiently (technically, it has a longer T_2 in these tissues). In a longer experiment the signal from a small, fast compartment could be drowned by the signal from slower compartments with greater affinity for isoflurane, lying closer to the surface coil. Our 6 cm surface coil was smaller relative to the brain than coils used in animal experiments so that it should have relatively more brain in its region of sensitivity, and our sampling rate of 2 min was shorter, making it easier to identify faster processes. Indeed, if we had continued to average over 4 min as in the pilot study, we may not have obtained statistical justification for biexponential elimination. Thus although the underlying kinetics in humans and animals are probably similar, different experimental designs have been biased towards different subprocesses.

Although we have data from only a few studies, our results match the expectation of practising anaesthetists and support the classical perfusion-limited pharmacokinetic theory of inhalation anaesthesia. We feel that because of the inherent risks of the study and the low yield, further human experiments should await improvement in the MRS technique.

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British Journal of Anaesthesia 1997; 79: 586–589

Magnetic resonance spectroscopy of isoflurane kinetics in humans. Part II: functional localization

G. G. Lockwood, D. P. Dob, D. J. Bryant, J. A. Wilson, J. Sargentoni, S. M. Sapsed-Byrne, D. N. F. Harris and D. K. Menon

Summary

We describe the first experiments to relate the cerebral kinetics of isoflurane (determined by fluorine magnetic resonance spectroscopy) to cerebral function. Using a surface receive coil we found two-compartment kinetics within the head with equilibrium half-times of 3.5 min and approximately 1 h with respect to expired isoflurane concentrations. Using critical fusion flicker frequency as an objective measure of the cerebral effect of isoflurane, we found evidence to identify the fast component as the brain. Responsiveness to command was lost at a brain partial pressure of 0.3% isoflurane. We conclude that the measured cerebral kinetics of isoflurane exactly matched the predictions of the classical perfusion-limited model. (*Br. J. Anaesth.* 1997; **79**: 586–589).

Key words
Anaesthetics volatile, isoflurane. Pharmacokinetics, isoflurane. Measurement techniques, magnetic resonance spectroscopy.

The tissue kinetics of isoflurane can be followed *in vivo* by fluorine magnetic resonance spectroscopy (^{19}F MRS). The first part of this study[1] reported the first such measurements in humans and demonstrated biexponential elimination from the head, which supports the predictions of the standard, perfusion-limited pharmacokinetic model. The concentration of isoflurane was too small to confirm spatial localization by ^{19}F magnetic resonance imaging, so in this part we report our experience with functional localization, that is relating tissue compartment concentrations of isoflurane deduced from MRS data to their cerebral effect. Such studies can only be performed in human subjects.

Subjects and methods

Most of the details of the subjects and methods have been reported in part I of this study[1]; only an overview and additional details are given here. In essence, volunteers were placed in a magnetic resonance spectrometer and breathed 0.6–1% isoflurane in oxygen. The end-expired isoflurane concentration was measured by an infrared analyser. A coil placed over their occiput collected MRS data. With this arrangement the amount of signal depends on the amount of isoflurane in the coil's receptive field, but the shape and regional sensitivity of this field is not known exactly.

Subjects were attended by two anaesthetists: one remained outside the spectrometer's radio frequency screening enclosure watching the electronic monitors, the other was inside the enclosure monitoring respiration and assessing the level of sedation by prompting the subject to press a communication bleeper at 1-min intervals. After the fourth experiment a system for monitoring critical flicker fusion (CFF) was included in the study. A red LED placed against a black background on the side wall of the bore of the magnet was observed by the subject who held a micro switch. Wires from these were passed through radio frequency filters to a computer which controlled the rate of flicker from outside the spectrometer. The flicker decreased by 1 Hz every second from 45 Hz until the subject pressed the micro switch to indicate that the flickering was visible. This fusion flicker frequency was stored on hard disk, the LED turned off for 3 s, then the process repeated. CFF is conventionally the average of fusion flicker (decreasing rate of flicker) and flicker fusion (increasing rate of flicker) frequencies. We were unable to measure the flicker fusion frequency contemporaneously because heavily sedated subjects confused flicker fusion runs with fusion flicker runs. The simple instruction to "Click when it flickers" was the most such subjects could manage in the relative isolation of the magnet bore.

An intra-arterial cannula was sited in four studies of three subjects. After a short period during which baseline measurements were made, a constant concentration of isoflurane (0.6–1%) was introduced into the inspired gas. Arterial blood analysis was used to confirm that the end-expired isoflurane concentration was being measured accurately in gas

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G. G. Lockwood, MB, BS, FRCA, BSC, D. P. Dob, BSC, MB, BS, FRCA, J. A. Wilson, FRCA, S. M. Sapsed-Byrne, AIBIOL, BSC, D. N. F. Harris, MD, FRCA (Department of Anaesthesia); D. J. Bryant, PHD, J. Sargentoni, DCR(R) MU (Robert Steiner Magnetic Resonance Unit); Hammersmith Hospital, London W12 0HS. D. K Menon, MB, BS, FRCA, MRCP, PHD, Department of Anaesthesia, Addenbrooke's Hospital, Cambridge. Accepted for publication: June 13, 1997.

aspirated along a 6-m catheter, using a technique similar to that described by Landon and colleagues[2] and modified later in our laboratory.[3]

A computer model of up to three parallel compartments was also developed in which the isoflurane partial pressure in each compartment was increased or decreased in proportion to the difference between the measured end-expired and modelled compartment partial pressures. Specifically:

$$P_i(t+1) = P_i(t) + (P\text{E}'(t) - P_i(t) \times k_i \times \delta_i$$

where $P\text{E}'(t)$ and $P_i(t)$=partial pressures in expired gas and the *i*th compartment, respectively at time *t*; k_i=compartment rate constant; δ_i=time interval between *t* and *t*+1. δ_i was 10 s—the interval between consecutive data sets from the gas analyser. The model total MRS signal is given by:

$$\text{MRS model}(t) = \Sigma^n{}_{i=1}\ W_i \times P_i(t)$$

where W_i=weighting factor of the ith compartment and *n*=number of compartments used in the model. The weighting factor may be considered as the product of a pharmacokinetic factor (which depends on the capacity of the compartment for isoflurane) and a spatial scaling factor (which depends on the regional sensitivity of the coil to the MR signal). These two components are constant in time. The least squares fit of the model to the actual MR data was made by manipulating one pair of variables for each compartment: the rate constant (k_i) and a weighting factor (W_i) for the contribution of that compartment to the total MRS signal. All modelling was performed by iteration using the Solver function of a Microsoft Excel v4 spreadsheet, with least squares solutions approximated from several initial variable values and checked visually to ensure that true minima had been found. The *F* test criterion of Boxenbaum, Riegelman and Elashoff[4] was used to determine the number of compartments appropriate for each subject's data.

The model enabled us to use all data acquired during complete studies, and the early data collected during studies which were terminated prematurely because of restlessness before wash-out data were collected. Furthermore, because the wash-in and wash-out data were modelled to the expired gas concentration, the effect of changes in ventilation on the elimination of isoflurane did not affect the rate constants for the compartments identified by the model.

During dynamic studies such as these, hysteresis between drug concentrations in different locations and their biological effect provide evidence of the site of drug action: lack of hysteresis is circumstantial evidence of site of effect. When CFF frequency results were available during both wash-in and wash-out they were plotted as functions of isoflurane concentrations in either expired gas or the tissue compartments and inspected for evidence of hysteresis.

We also sought evidence of hysteresis between losing and gaining responsiveness to command. The actual brain isoflurane concentrations at these moments should have small variance. We therefore normalized each group of data (expired gas, fast and slow compartments) by dividing by its mean and compared variances by the *F* test.

Results

A total of eight studies were undertaken on five volunteers (see table 1). Expired isoflurane concentrations were not stored during our pilot study, and therefore these data cannot be used here. Only four studies produced both wash-in and wash-out MRS data and an example is shown in figure 1. In most instances the other studies were terminated prematurely because the subject became restless before regaining consciousness. When this happened the subject was withdrawn immediately from the magnet bore and wash-out data were lost. In one study the first measured ^{19}F signal was greater than those immediately after. Although no cause could be found at the time, this was assumed to be a technical problem and the study was abandoned. For safety, the subject was removed from the magnet bore and allowed to recover under direct observation so that wash-out data could not be acquired. Analysis of those MRS data (excluding the first measurement)

Table 1 Results of the eight studies undertaken in five volunteers

Subject No.	No. of data points	$T_{1/2}$, fast	$T_{1/2}$, slow	Signif. of two compartments	Comments
1	—	—	—	—	Expired gas not measured so data not usable here
2	22	5.9	96	0.001	Complete MRS data set
1	40	1.8	65	0.001	Complete MRS data set
2	8	—	48	ns	No wash-out data (study terminated because of presumed technical failure)
1	22	2.4	41	0.001	No wash-out data (subject removed from scanner because of movement). CFF data collection continued and analysed against extrapolated fast compartment signal
3	13	—	30	ns	Subject moved while heavily sedated and so withdrawn briefly from spectrometer before a second attempt, also unsuccessful. Procedure abandoned and no wash-out data collected. Both wash-in data sets analysed together
4	21	—	16	ns	Complete MRS data set. Baseline CFF too variable to make data useful
5	19	3.9	263	0.005	Complete MRS data set. Consistent CFF
Group	145	4.8	135	0.00001	The best fit when the two-compartment model for each data set was constrained to share group half-times

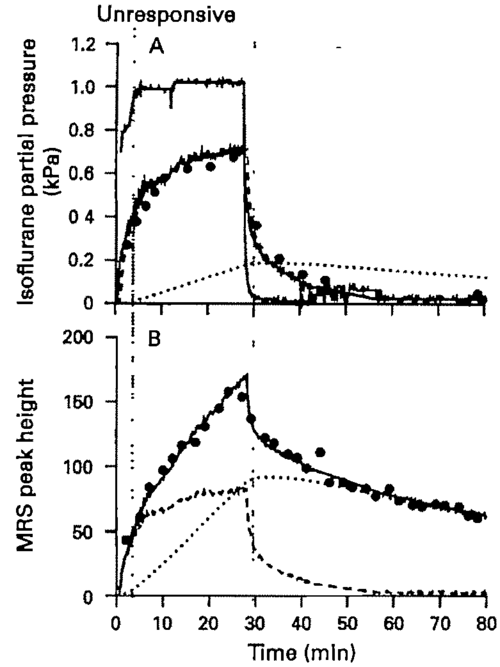

Figure 1 An example study (subject No. 2). A: Partial pressure of isoflurane measured in inspired gas (upper continuous line), expired gas (lower continuous line) and arterial blood (●). Broken and dotted lines show the partial pressure of isoflurane calculated to be in the fast and slow compartments, respectively, as derived from the magnetic resonance (MR) data. B: Actual MR data in arbitrary units (circles), the total of the two-compartment model (continuous line) and the fast (broken line) and slow (dotted line) components of the model.

showed single compartment kinetics and it seems likely that signal was received initially from the fast compartment but then the subject moved, displacing the surface coil so that it collected data from superficial tissues only.

Arterial partial pressures were measured in four studies of three subjects. During wash-in, values were 80–95% of end-expired partial pressures. There was a similar, but reversed, gradient during wash-out.

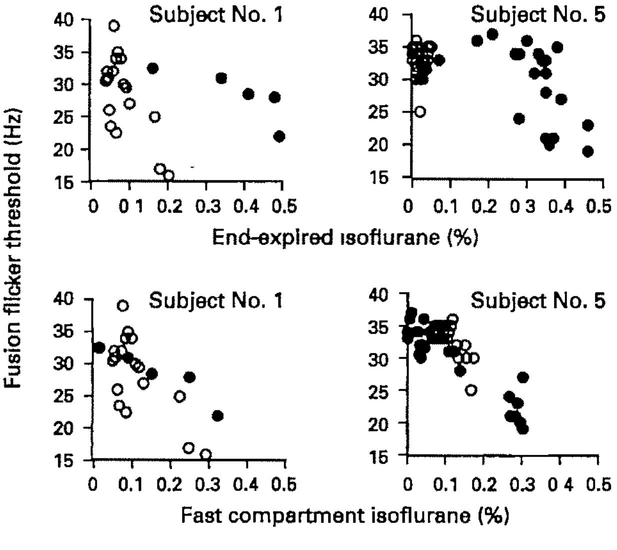

Figure 2 Critical fusion flicker (CFF) frequencies for two subjects (Nos 1 and 5) from whom data were available during both wash-in and wash-out of isoflurane. In the upper plots CFF is displayed as a function of isoflurane measured in expired gas, in the lower plots as a function of isoflurane concentration calculated to be in the fast component, as derived from magnetic resonance data. Solid symbols indicate data recorded during wash-in, open symbols during wash-out. Note that the obvious hysteresis in the upper plots is absent in the lower plots.

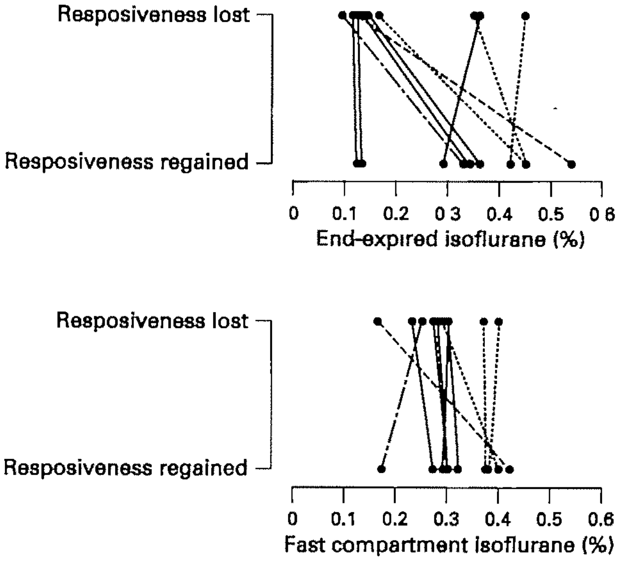

Figure 3 Isoflurane concentrations in end-expired gas and the fast component (calculated from the magnetic resonance data) at the moments of losing and next regaining responsiveness to command. Data from four subjects, two of whom aroused spontaneously during the study and contributed multiple data points (—=subject No. 1; -·-=subject No. 2; ...=subject No. 4; continuous=subject No. 5).

Four of the seven sets of data modelled against expired isoflurane concentration supported a two-compartment model ($P<0.005$), giving a mean of 3.5 min for the fast half-time (table 1). As both wash-in and wash-out measurements took place over a 40-min period each, processes with half-times greater than this period were poorly determined. No data set supported a three-compartment model. When the data were pooled, two-compartment models were strongly supported over one-compartment models ($P<0.00001$) with group rate constants equivalent to half-times of 4.8 and 135 min.

Only two studies produced CFF data during both wash-in and wash-out. These are shown together in figure 2. Hysteresis is clearly present in the plot of CFF against expired isoflurane, but this is absent when CFF is plotted against isoflurane in the fast compartment.

Four subjects lost and regained responsiveness to command while in the spectrometer (fig. 3), two of these on more than one occasion as irregular respiration caused the expired isoflurane concentration to increase and decrease. When normalized by division by the group mean, the variance in the fast compartment was less than in the expired gas ($P<0.0005$) or the slow compartment ($P<0.00001$).

Discussion

The difficulties of clinical monitoring of patients in a spectrometer are now well understood and relatively easy to overcome.[5] Assessment of the conscious level of a subject in the magnet bore who cannot speak because of the mouthpiece, and is in any case required to keep as still as possible, remains troublesome and limits pharmacodynamic conclusions. As a crude indicator of consciousness, subjects operated a whistle by squeezing a hand-held bulb in response to a command from the attending anaesthetist. This requires consistent verbal delivery of the command which must gain the subject's attention without startling him (which could precipitate movement). CFF is a more refined measure of cognitive impairment and was introduced later in the series of experiments. We decided that alternatives such as response time would risk movement artefact in sedated subjects.

Respired gas was sampled close to the mouth from a breathing system which depended on careful placement and facial tone to maintain a seal at the mouth. The sample was obtained along a 6-m line, which increases both transit and response times of the Datex Ultima. The accuracy of our measurements of isoflurane in end-expired gas is therefore open to question, so we obtained frequent arterial blood samples during four studies. In general we found that during wash-in arterial partial pressures followed measured expired gas partial pressures with a brief lag and small gradient, similar to the findings of other investigators.[6 7]

We have found evidence of two tissue compartments filling from the isoflurane tension in alveolar gas. The surface coil we used collected MRS data from a region of the head, including skin, fat, bone and brain, by acting as an aerial over the occiput. Three factors affect the fluorine MRS signal received from each tissue: the concentration of isoflurane within the tissue, its proximity to the receive coil and the chemical environment of the fluorine atoms in that tissue. Pharmacokinetic theory can predict the concentration of isoflurane in each tissue, but the contribution to the total MRS signal cannot be determined *a priori*. The weights calculated for each compartment therefore hold no clue as to their physical representation which remains undetermined because the MRS signal in our experiments was too weak to allow imaging. Our data strongly support the brain as the source of the fast compartment signal because (i) the kinetics of our model matched well those predicted by classical pharmacokinetic theory; (ii) the hysteresis observed when CFF was related to expired gas was lost when it is related to the fast compartment (although these data came from only two subjects); (iii) the moments of losing and regaining responsiveness were related to a relatively constant fast component isoflurane concentration. Although marked variation in anaesthetic distribution within the brain has been demonstrated on a small scale,[8] there is no evidence to suggest the existence of two compartments large enough to be detected by the spectrometer yet having such different kinetics. Anaesthetics are generally approximately half as soluble in grey as in white matter[9] so even with its greater perfusion,[10] the grey matter should equilibrate no more than six times faster. The fact that we obtained a fluorine signal from a single compartment when the coil was displaced also suggests that the slow compartment is superficial and spatially separated from the brain.

Although we have few complete studies they are in close agreement and are supported by our other results. The fast compartment correlates with objective measures of anaesthetic effect. We have sufficient confidence in these data to believe that further repetition—with the potential risks to the subjects—is not justified until technical improvements allow localization of the signal. Our findings support the classical perfusion-limited pharmacokinetic theory of inhalation anaesthesia.

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Differential effects of nitrous oxide and propofol on myogenic transcranial motor evoked responses during sufentanil anaesthesia†

L. H. UBAGS, C. J. KALKMAN, H. D. BEEN AND J. C. DRUMMOND

Summary

We have compared the effects of 50% nitrous oxide and propofol, each administered concurrently with sufentanil, on the amplitudes and latencies of the compound muscle action potential (CMAP) response to transcranial electrical stimulation. Using a crossover design, 12 patients undergoing spinal surgery were exposed to both 50% nitrous oxide and propofol, the latter in a bolus–infusion regimen. Six patients received nitrous oxide first and six received propofol first. CMAP were recorded from the tibialis anterior muscle in response to both single and paired transcranial electrical stimuli. With single pulse stimulation, median CMAP amplitude was significantly greater during administration of nitrous oxide than propofol (nitrous oxide 335 (10th–90th percentiles 35–849) µV; propofol 36 (0–251) µV) ($P<0.01$). With paired stimulation, there was no significant difference in CMAP amplitude during the two regimens (nitrous oxide 1031 (296–1939) µV; propofol 655 (0–1867) µV). The results indicate that propofol caused more depression of transcranial electrical motor evoked responses than 50% nitrous oxide but that the difference was probably clinically unimportant when a paired stimulation paradigm was used. (*Br. J. Anaesth.* 1997; **79**: 590–594).

Key words

Brain, evoked potentials. Spinal cord, evoked potentials. Monitoring, evoked potentials. Anaesthetics gases, nitrous oxide. Anaesthetics i.v. propofol. Analgesics opioid, sufentanil.

Intraoperative monitoring of motor evoked responses to transcranial electrical or magnetic stimulation (tc-MER) provides a method of assessing the integrity of ventral motor columns during operations in which there is a risk of spinal cord injury.

A difficulty with intraoperative tc-MER monitoring lies in the considerable tc-MER amplitude depression that occurs with most anaesthetic regimens. At least with single stimuli, the use of relatively low concentrations of volatile anaesthetics (0.2–0.3% end-tidal isoflurane[1 2]) precludes intraoperative tc-MER monitoring. Nitrous oxide,[3] benzodiazepines,[4 5] barbiturates and propofol[5] have been shown to depress tc-MER amplitude. Drugs that have been shown to have only minor effects on tc-MER are those known to maintain or increase muscle tone, for example etomidate,[5] ketamine and synthetic opioids.[5]

Currently, two anaesthetic regimens are used widely during surgery in which myogenic responses to transcranial stimulation are used for spinal cord motor tract monitoring. Some groups have successfully used nitrous oxide–opioid anaesthesia.[2 3 6] Others have advocated propofol–opioid total i.v. anaesthesia (TIVA).[7] These two anaesthetic techniques have not been compared previously with respect to the relative magnitude of tc-MER depression.

The purpose of this crossover study was to determine the relative effects of nitrous oxide and propofol on tc-MER amplitude, amplitude variability and onset latencies. As it was shown recently that multiple stimuli may improve the efficiency of transcranial stimulation,[8–11] comparison of the two anaesthetic regimens was performed with both single and paired stimuli.

Patients and methods

Written informed consent for this institutionally approved study was obtained from 12 patients (seven females, aged 14–64 yr) undergoing orthopaedic spinal surgery.

Transcranial stimulation was performed using two identical Digitimer D180A transcranial electrical stimulators (Digitimer Ltd, Welwyn Garden City, UK), triggered either simultaneously (single pulse stimulation) or sequentially with an inter-stimulus interval of 3 ms (paired stimulation). The outputs from both units were combined via diodes and delivered to the scalp via 9-mm silver EEG disk

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LEON H. UBAGS, MD, COR J. KALKMAN, MD, PHD (Department of Anaesthesiology); HENK D. BEEN, MD, PHD (Department of Orthopaedics); Academic Hospital, University of Amsterdam, PO Box 22700, 1100 DE Amsterdam, The Netherlands. JOHN C. DRUMMOND, MD, Department of Anesthesiology, University of California at San Diego, VA Medical Center, San Diego, CA, USA. Accepted for publication: July 15, 1997.

Correspondence to C. J. K.

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electrodes. The anode was positioned at Cz and the cathode consisted of interconnected electrodes at Fz, A1 and A2 (international 10–20 system).[12] Myogenic responses were recorded over the left and right tibialis anterior muscles, using adhesive gel silver–silver chloride electrodes (Cleartrace, Medtronic Andover Medical Inc., Haverhill, MA, USA). The active electrode was placed over the muscle belly, referenced to an electrode placed over the tendon. The signal was amplified 5000–20 000 times (adjusted to obtain maximum vertical resolution), and filtered between 30 and 1500 Hz using a 3T PS-800 biologic amplifier (Twente Technology Transfer, Twente, The Netherlands). These amplifiers have a very high input impedance ($>10^{12}$ Ω) and common mode rejection ratio (greater than 95 dB). The responses were sampled at 2 kHz, displayed and stored on a Macintosh Quadra computer (Apple Computer, Cupertino, CA) with 12 bit A/D conversion and MER acquisition software written with the LabView data acquisition development system (National Instruments, Austin, TX, USA).

In both groups anaesthesia was induced with etomidate 0.3 mg kg^{-1} and a loading dose of sufentanil 1.5 μg kg^{-1}, followed by continuous infusion of 0.5 μg kg^{-1} h^{-1}. Intubation of the trachea was facilitated by vecuronium 0.1 mg kg^{-1}. Neuromuscular block was monitored electromyographically at the hypothenar eminence using a Datex Relaxograph (Datex, Finland). This device applies a train-of-four stimulus to the ulnar nerve every 20 s and displays the height of the first response (T1 %), and the train-of-four ratio (T4/T1 %). After the amplitude of T1 had recovered to 20% of control, neuromuscular block was maintained at this level throughout surgery with vecuronium using a closed-loop infusion system. This level of neuromuscular block at the hypothenar muscle produces a T1 of 60% at the tibial anterior muscle.[13]

Routine anaesthetic monitoring included ECG, Sp_{O_2}, invasive arterial pressure, central venous pressure, end-tidal carbon dioxide concentration and nasopharyngeal temperature.

The order in which patients received nitrous oxide or propofol was randomized. After induction of anaesthesia, 50% of patients received 50% nitrous oxide in oxygen until 60 min after skin incision. Thereafter, administration of nitrous oxide was discontinued and propofol 1 mg kg^{-1} administered i.v., followed by an infusion at a rate of 10 mg kg^{-1} h^{-1} for the first 10 min, 8 mg kg^{-1} h^{-1} for the next 10 min and 6 mg kg^{-1} h^{-1} for the remainder of the procedure. This infusion results in blood propofol concentrations of approximately 3 μg ml^{-1}.[14]

In the other six patients, anaesthesia was maintained initially with propofol, using the infusion regimen described above. Sixty minutes after skin incision, the propofol infusion was discontinued and replaced by 50% nitrous oxide in oxygen.

Tc-MER stimulus intensity was determined after induction of anaesthesia with etomidate and was set at just supramaximal to single pulse stimulation (typically 500–700 V). The tc-MER recordings were made over a 30-min period, starting at least 20 min after skin incision, or 30 min after the crossover. Compound muscle action potentials (CMAP) to single and paired stimulation were acquired in a 1-min period every 3 min during the study. For each regimen and stimulation paradigm, the median amplitude from 10 responses, recorded every 3 min, was calculated and compared using the Wilcoxon signed rank test. Amplitudes are presented as median (10th and 90th percentiles) and latencies as mean (SD).

To estimate within-patient variability, we calculated the coefficient of variation (cv) from 10 responses. The cv were compared using the Wilcoxon signed rank test and are expressed as median (10th and 90th percentiles).

Each patient was questioned specifically for recall of intraoperative events immediately after surgery and on the following day.

Results

Figure 1 shows representative triplicate CMAP to paired and single pulse transcranial stimulation during both anaesthetic regimens in one patient.

SINGLE PULSE STIMULATION

During nitrous oxide–opioid anaesthesia, reproducible responses with single transcranial stimuli were recorded in 11 of 12 patients, whereas during propofol–opioid TIVA, tc-MER were recordable in seven of 12 patients. During the nitrous oxide regimen, tc-MER amplitude was 335 (35–849) μV and latency to onset 33.9 (3.9) ms. With propofol, tc-MER amplitude was 36 (0–251) μV ($P<0.01$) and latency 34.4 (3.4) ms. There was no significant difference in onset latency between the two anaesthetic regimens.

PAIRED STIMULATION

During nitrous oxide–opioid anaesthesia, tc-MER to paired stimulation were recordable in all patients, whereas tc-MER during propofol–opioid anaesthesia were elicited in 10 of 12 patients with paired stimuli. There was no significant difference in amplitude or onset latency between the two anaesthetic regimens. During the nitrous oxide regimen, tc-MER

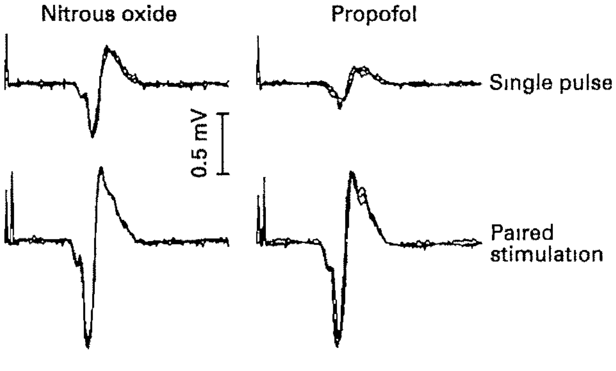

Figure 1 CMAP to paired and single pulse transcranial stimulation, during both anaesthetic regimens (nitrous oxide and propofol), in a patient undergoing orthopaedic spinal surgery Triplicate responses are superimposed to indicate reproducibility.

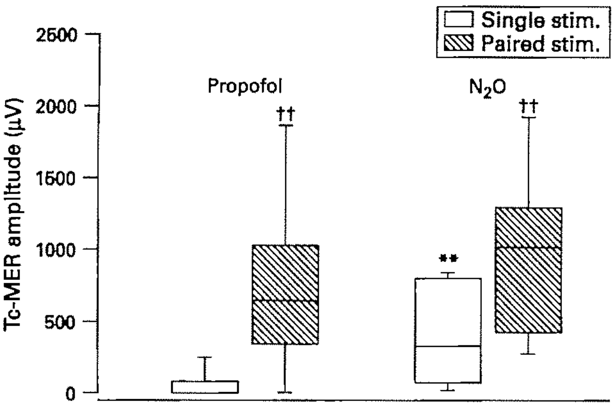

Figure 2 Box plots of tibialis anterior tc-MER amplitude to single or paired transcranial electrical stimulation during both anaesthetic regimens (nitrous oxide (N_2O) and propofol). Horizontal bars represent 90, 75, 50 (median), 25 and 10th percentiles. $^{**}P<0.01$ compared with propofol; $^{††}P<0.01$ compared with single pulse stimulation.

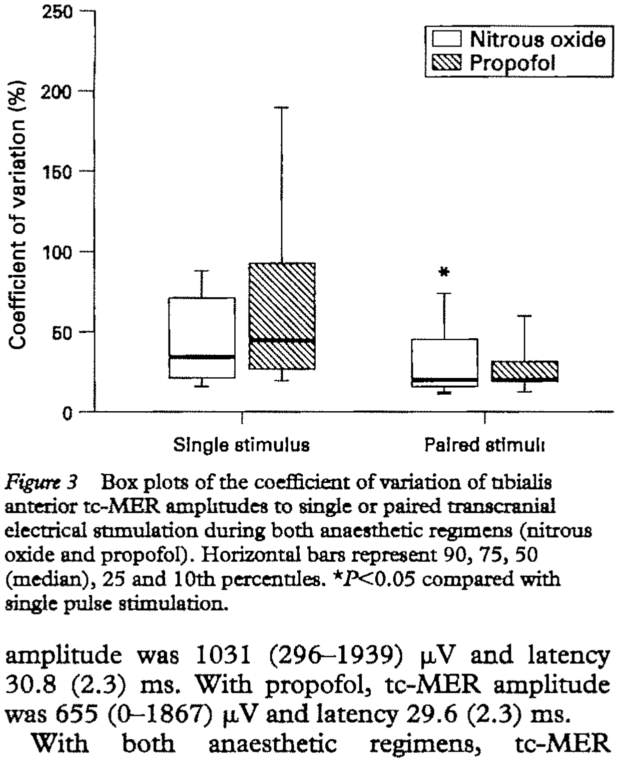

Figure 3 Box plots of the coefficient of variation of tibialis anterior tc-MER amplitudes to single or paired transcranial electrical stimulation during both anaesthetic regimens (nitrous oxide and propofol). Horizontal bars represent 90, 75, 50 (median), 25 and 10th percentiles. $^{*}P<0.05$ compared with single pulse stimulation.

amplitude was 1031 (296–1939) μV and latency 30.8 (2.3) ms. With propofol, tc-MER amplitude was 655 (0–1867) μV and latency 29.6 (2.3) ms.

With both anaesthetic regimens, tc-MER amplitude was significantly higher when paired transcranial stimulation was used ($P<0.01$) and onset latency was shorter ($P<0.01$). Figure 2 shows box plots of tibialis anterior tc-MER to single pulse and paired transcranial stimulation during both anaesthetic techniques.

There was no significant difference in the coefficient of variation for tc-MER amplitude between the two anaesthetic regimens (fig. 3). For the nitrous oxide–opioid regimen, cv was significantly less ($P<0.05$) with paired stimuli than with a single stimulus. During the propofol–opioid regimen there was a tendency ($P=0.08$) to a smaller cv with paired stimulation. With a single stimulus, the cv was 32% (12–85%) during nitrous oxide–opioid anaesthesia and 42% (15–190%) during propofol–opioid TIVA. When paired stimuli were used, the cv was 8% (18–71%) during nitrous oxide–opioid anaesthesia and 14% (9–57%) during propofol–opioid TIVA.

During the recording period, haemodynamic variables remained stable and there was no significant difference in heart rate (HR) or mean arterial pressure (MAP) between the two anaesthetic regimens. During propofol–opioid anaesthesia, mean HR was 76 (SD 6.4) beat min^{-1} and MAP 83 (10.1) mm Hg; during nitrous oxide–opioid anaesthesia, HR was 78 (8.2) beat min^{-1} and MAP 81 (12.3) mm Hg. None of the patients experienced recall of intraoperative events.

Discussion

The data derived from this study indicate that at the doses used, propofol–opioid TIVA depressed the amplitude of myogenic responses to electrical transcranial stimulation more than nitrous oxide–opioid anaesthesia. Although there was no significant difference in amplitude between both anaesthetic regimens when paired transcranial stimuli were used, tc-MER were not recordable in two of 12 patients during propofol, while during nitrous oxide, tc-MER were recordable in all patients. Although nitrous oxide is a potent depressant of myogenic tc-MER, most authors were successful in obtaining reproducible myogenic responses to transcranial stimulation, provided relatively low concentrations of nitrous oxide were used. Zentner and Ebner have examined the effects of increasing nitrous oxide concentrations on motor evoked responses to cortical and mid-cervical electrical stimulation, recorded from the thigh muscles in six rats.[15] They observed a 45% reduction in amplitude with an end-tidal nitrous oxide concentration of 50%; at 66% end-tidal nitrous oxide, the myogenic signal was completely abolished.

Ghaly and co-workers have examined the effects of nitrous oxide on magnetic tc-MER recorded from the fore- and hindlimb flexor muscles in 16 cynomolgus monkeys. They were able to record tc-MER in all animals with nitrous oxide concentrations up to 75%. However, with 75% end-tidal nitrous oxide, tc-MER amplitude was significantly decreased and stimulation threshold intensity increased, compared with 25% and 50% end-tidal nitrous oxide.[16]

Woodforth and colleagues studied variability of tibialis anterior tc-MER to electrical stimulation in six patients undergoing surgery for correction of scoliosis.[17] Anaesthesia was maintained with fentanyl and 70% nitrous oxide in oxygen. The authors recorded responses to single pulse stimulation in all patients although amplitude was very low (mean of 100 responses <50 μV in all patients). However, with these high concentrations nitrous oxide tc-MER amplitude is depressed substantially and variability increases to such an extent that reliable spinal cord monitoring may not be possible.

In contrast, most studies which have described clinical tc-MER monitoring during propofol anaesthesia showed a smaller success rate in obtaining a reproducible myogenic response. Kalkman and co-workers examined the effects of a bolus dose of propofol 2 mg kg^{-1} on electrical and magnetic tibialis anterior tc-MER in five healthy volunteers.[5]

Two minutes after administration of propofol tc-MER amplitude decreased to 2.2 (SD 0.9) % of baseline; 30 min after administration, tc-MER amplitude was still depressed (44 (18) %). There was no effect on onset latency.

Jellinek, Jewkes and Symon studied tc-MER in 26 patients undergoing surgery for a unilateral prolapsed disc during propofol TIVA.[7] CMAP to electrical transcranial stimulation were recorded from the first dorsal interosseous muscle of the foot of the asymptomatic leg or from the second dorsal interosseous muscle of the hand. After an induction dose of 2 mg kg^{-1}, anaesthesia was maintained with a continuous infusion at a rate of 10–12 mg kg^{-1} h^{-1}. They were able to elicit reproducible tc-MER in 23 of 26 patients (88.5%), but tc-MER amplitude was 7% of awake control values (obtained with a magnetic transcranial stimulator).

Taniguchi and colleagues studied the effects of propofol on magnetic tc-MER recorded from the abductor pollicis brevis muscle in 22 patients undergoing surgery for lumbar disc herniations.[18] They used a fixed infusion scheme, designed to reach a plasma propofol concentration of 1.5 $\mu g\ ml^{-1}$ within 15 min. Fifteen minutes after the start of propofol infusion (cumulative dose 128 mg) tc-MER were preserved in only three of 22 cases (14%). Jones and colleagues were able to record reproducible myogenic responses of at least 100 μV to trains of three to six transcranial responses during propofol–nitrous oxide–alfentanil anaesthesia, whereas single pulse stimulation failed to elicit reproducible responses.[19]

It is conceivable that the propofol–opioid and the nitrous oxide–opioid regimens were not equipotent and that the propofol–opioid regimen used in this study provided a deeper level of anaesthesia than the nitrous oxide–opioid technique. This could explain the observed difference in tc-MER amplitudes during both anaesthetic regimens. It is likely that a deeper level of anaesthesia results in more amplitude depression because most anaesthetics that depress tc-MER do so in a dose-dependent manner. Unfortunately, there is no method to reliably quantify the "level of anaesthesia" in a clinical setting and we are therefore unable to determine if the observed differences in tc-MER depression were the result of a difference in depth of anaesthesia. The analgesic component consisted of constant infusions of sufentanil and was similar in both regimens. Inadequate anaesthesia, as suggested by increases in heart rate and arterial pressure, did not occur during each regimen and no patient had recall of intraoperative events.

This study confirms previous results that the use of paired transcranial stimulation partly overcomes the anaesthetic-induced depression of the myogenic response during nitrous oxide–opioid[10] and isoflurane anaesthesia.[11] The observed amplitude augmentation with paired stimuli is most likely the result of temporal summation; the first stimulus lowers the excitation threshold of the cortical and spinal motor neurones, thereby facilitating initiation of neuronal discharge by the second stimulus.[10] It is conceivable that stimulation with more than two successive pulses might further increase intraoperative tc-MER amplitudes and result in a greater success rate of tc-MER monitoring during propofol–opioid anaesthesia. Kawaguchi and co-workers described the effects of single pulse and train-of-five electrical stimulation of the exposed motor cortex on the tibialis anterior myogenic response during an anaesthetic regimen consisting of nitrous oxide and isoflurane or sevoflurane.[11] With train-of-five stimulation they were able to record tc-MER in all patients with concentrations of the volatile anaesthetic up to 1.5 times the minimum alveolar concentration.

The results of this study also suggest that the reproducibility of myogenic tc-MER increases when paired stimuli are used. Within-patient variability, expressed as cv, decreased when two pulses were used; this decrease was more pronounced during nitrous oxide–opioid anaesthesia than during propofol–opioid TIVA. It is likely that the decrease in cv during opioid–propofol TIVA was not statistically significant because of the small number of patients analysed (five patients had no response to a single stimulus during TIVA). It is conceivable that reproducibility increases because a higher tc-MER amplitude is obtained that is closer to the maximal response that can be obtained (the CMAP that results when all motor units are discharged).

In summary, we have demonstrated that during propofol–opioid TIVA, muscle responses to electrical transcranial stimulation were depressed more than during nitrous oxide–opioid anaesthesia. However, when paired stimulation was used, responses during both anaesthetic regimens were amplified considerably and the difference became clinically irrelevant in most patients. This suggests that when tc-MER monitoring is indicated, and there is concern about the adequacy of nitrous oxide–opioid anaesthesia, it is possible to use propofol–opioid TIVA, provided that a multiple stimulus paradigm is used. In a subset of patients, propofol–opioid TIVA may depress the motoneural system to such an extent that recordable tc-MER cannot be obtained, even when paired stimuli are used. When this occurs propofol may be substituted by nitrous oxide to allow tc-MER monitoring during stages of surgery in which spinal cord monitoring is imperative. Furthermore, it is likely that the use of more than two successive stimuli may increase the success rate of intraoperative tc-MER monitoring during propofol–opioid TIVA. The results of this study justify further clinical evaluation of the efficacy of multi-pulse transcranial stimulation during total i.v. anaesthesia.

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Emergence times from xenon anaesthesia are independent of the duration of anaesthesia†

T. GOTO, H. SAITO, Y. NAKATA, S. UEZONO, F. ICHINOSE AND S. MORITA

Summary

Xenon (MAC=71%) has an extremely low blood:gas partition coefficient (0.14). Therefore, we predicted that the rate of emergence from xenon anaesthesia would not be affected greatly by duration of anaesthesia. We studied 54 ASA I–II patients undergoing lower abdominal surgery who received equal MAC anaesthesia with 60% xenon, 60% nitrous oxide with 0.5% isoflurane or 60% nitrous oxide with 0.7% sevoflurane (n=18 per group), each supplemented with extradural mepivacaine anaesthesia. Duration of anaesthesia was 58–380 min. At the end of operation, all inhalation anaesthetics were discontinued and patients were allowed to wake up while breathing oxygen spontaneously. A blinded investigator recorded the time until patients opened their eyes on command (T1), were judged ready for tracheal extubation (T2), could correctly state their name, date of birth and name of the hospital (T3), and could count backwards from 10 to 1 in less than 15 s (T4). Emergence times after xenon and nitrous oxide–sevoflurane anaesthesia did not correlate with duration of anaesthesia, whereas those from nitrous oxide–isoflurane had positive correlations. Mean emergence times from xenon anaesthesia were: T1, 3.3 (SD 1.0) min; T2, 3.6 (1.0) min; T3, 5.0 (1.1) min; and T4, 6.2 (1.7) min. These values were approximately 50% of those after nitrous oxide–sevoflurane anaesthesia (T1, 5.6 (1.4) min; T4, 10.5 (2.0) min). We conclude that xenon provided fast emergence from anaesthesia, regardless of the duration of anaesthesia. (*Br. J. Anaesth.* 1997; **79**: 595–599).

Key words
Anaesthesia, duration. Recovery, postoperative. Anaesthetics gases, nitrous oxide. Anaesthetics gases, xenon. Anaesthetics volatile, isoflurane. Anaesthetics volatile, sevoflurane.

Xenon, an inert gas with a clinically relevant anaesthetic potency (MAC=71%),[1] is extremely insoluble in human body tissues. Its blood:gas partition coefficient is 0.14,[2] significantly lower than those of other inhalation anaesthetics, including nitrous oxide (0.47), sevoflurane (0.65) and desflurane (0.42).[3] This property predicts that emergence from xenon anaesthesia is faster than that from other inhalation anaesthetics (which we demonstrated previously to be the case[4]), and that it is influenced less by duration of anaesthesia.[5] In order to test the latter prediction, we conducted a randomized, controlled study to examine the correlations between duration of anaesthesia and emergence times in patients anaesthetized with equal MAC xenon, nitrous oxide–sevoflurane or nitrous oxide–isoflurane for various lengths of time.

Patients and methods

The methods were similar to those of our previous investigation[4] with slight modifications.

After written informed consent was obtained, we studied 54 ASA I or II patients of both sexes, aged 32–64 yr, undergoing elective lower abdominal surgery (mainly gynaecological procedures) according to a design approved by the Institutional Human Studies Committee of Teikyo University. Patients with pulmonary, cardiovascular, hepatic, renal or neurological diseases were excluded. Also excluded were patients receiving medications known to influence anaesthetic or analgesic requirements and those who had contraindications to extradural anaesthesia (e.g. coagulopathy, history of allergic reactions to local anaesthetics, patient's refusal). Preanaesthetic laboratory values were within normal limits.

When the unpremedicated patient arrived in the operating theatre, midazolam 30 $\mu g\ kg^{-1}$ was administered i.v. An extradural catheter was placed at the L2–3 interspace, through which 1.5% mepivacaine with adrenaline 1:200 000 were administered, 3 ml as a test dose, followed 3 min later by an additional 9–12 ml depending on the height of the patient. If a sensory level to pinprick of T10 or higher was not obtained within 15 min, the extradural catheter was judged to be functioning inadequately and the patient was excluded from the study. A well-functioning extradural catheter was

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TAKAHISA GOTO, MD, YOSHINORI NAKATA, MD, MBA, SHOICHI UEZONO, MD, FUMITO ICHINOSE, MD, SHIGEHO MORITA, MD (Department of Anaesthesia); HAYATO SAITO, BS (Department of Medical Engineering); Teikyo University, School of Medicine, Ichihara Hospital, 3426–3 Anesaki, Ichihara, Chiba 299–01 Japan. Accepted for publication: June 20, 1997.

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Correspondence to T. G.

regarded as an essential component of our anaesthetic technique because of the MAC value of xenon (71%) and our desire to avoid other systemic supplementations while assuring patient comfort.

Patients were allocated randomly to one of three anaesthetic treatment groups: xenon, nitrous oxide–sevoflurane or nitrous oxide–isoflurane ($n=18$ per group). General anaesthesia was induced with fentanyl 2 μg kg^{-1} and thiopentone 4 mg kg^{-1} i.v., and the trachea was intubated with the aid of vecuronium 10 mg i.v. Patients were then denitrogenated for 30 min using an inflow of oxygen 8 litre min^{-1} in order to suppress nitrogen accumulation within the system during subsequent closed-circuit anaesthesia.[6] During this denitrogenation period, anaesthesia was maintained with 1% isoflurane (xenon and nitrous oxide–isoflurane groups) or 1.8% sevoflurane (nitrous oxide–sevoflurane group). The end-tidal concentration of carbon dioxide (E'_{CO_2}) was maintained at 4.0–4.7 kPa with mechanical ventilation. If clinically indicated, adrenaline 4–8 mg or phenylephrine 50–100 μg were administered i.v. to maintain systemic arterial pressure at acceptable levels.

Routine monitoring devices included an oesophageal stethoscope with a temperature sensor, ECG (lead II), automated arterial pressure cuff and pulse oximeter. End-tidal concentrations of nitrous oxide, carbon dioxide, sevoflurane and isoflurane were monitored continuously with an infrared gas analyser (PM 8050, Drägerwerk, Lübeck, Germany). The end-tidal concentration of xenon was monitored continuously using a xenon analyser (Anzai Medical, Tokyo, Japan), which was calibrated before each case with the use of an 80% xenon–20% oxygen mixture analysed to ±0.02% accuracy (Nihon-Sanso, Tokyo, Japan). The effective working range for this monitor was 1–100% with an error of ±1% and 90% response time of less than 1 s.

Thirty minutes after induction of anaesthesia when denitrogenation was complete, xenon, nitrous oxide–isoflurane or nitrous oxide–sevoflurane was started. For the xenon patients, oxygen was stopped and the upright ventilator bellows was deflated completely and refilled quickly with 100% xenon. Xenon was then started at 2 litre min^{-1}. Two to three minutes later when the end-tidal concentration reached 60%, xenon flow was reduced, oxygen was resumed and the anaesthesia system was closed in order to minimize subsequent expenditure of xenon. During closed-circuit anaesthesia, fresh inflow rates of xenon and oxygen were adjusted to maintain the end-tidal concentration of xenon at 60%. Xenon inflow was recorded every minute in seven patients for whom the anaesthesia system was made highly leak-free (leak <30 ml min^{-1} at a constant circuit pressure of 20 cm H_2O). When the end-tidal oxygen concentration decreased to less than 20% because of accumulation of nitrogen, the system was flushed with a 60% xenon–40% oxygen mixture. Although no additional volatile anaesthetic was administered after xenon was started, our pilot study revealed that 0.1–0.2% isoflurane was always detected in the system, presumably because the isoflurane vapour contained within the patient's lungs at the time of circuit closure was retained in the breathing system. Therefore, it was estimated that patients in the xenon group were receiving approximately 0.9 MAC of anaesthesia, assuming additivity of MAC, because xenon and isoflurane provided $60/71=0.84$ and $0.1/1.15=0.085$ MAC, respectively. In order to provide the same MAC fractions in the nitrous oxide–sevoflurane and nitrous oxide–isoflurane groups, end-tidal concentrations of nitrous oxide, sevoflurane and isoflurane were maintained at 60%, 0.7% and 0.5%, respectively.[3 7] The total inflow of 3 litre min^{-1} was used in the nitrous oxide–volatile anaesthetic groups.

In addition, all patients received continuous extradural infusion of 1.5% mepivacaine containing adrenaline 1:200 000 at 6 ml h^{-1}, started immediately after induction of anaesthesia. When xenon or nitrous oxide was started, the extradural infusion rate was adjusted to maintain mean arterial pressure and heart rate within 20% of preoperative values. Additional doses of vecuronium or pancuronium were administered if indicated clinically. Body temperature was maintained with the use of a warming mattress placed on the operating table. I.v. fluids were also warmed.

Before skin closure, residual neuromuscular block was antagonized by neostigmine 2.5 mg and atropine 1.0 mg i.v., and spontaneous ventilation was allowed to return. At the end of operation, all inhalation anaesthetics were discontinued and oxygen 8 litre min^{-1} was administered. E'_{CO_2}, ventilatory frequency and oesophageal temperature were recorded at this time. An investigator who was blinded to the anaesthetic regimen administered recorded the times from discontinuation of the anaesthetics until patients opened their eyes on verbal command and were judged ready for extubation (i.e. in addition to opening eyes, they either squeezed the investigator's hand or took a deep breath on command and showed a regular breathing pattern). Furthermore, times when patients regained orientation, that is when they were able to correctly state their name, date of birth and name of the hospital, were recorded. Finally, times when patients could count backwards from 10 to 1 in less than 15 s were recorded. These emergence times were assessed at either 30-s (eye opening and extubation) or 60-s (orientation and counting backward) intervals. Fifteen minutes after tracheal extubation when the continuous extradural infusion was stopped, extradural block level to pinprick was examined, and patients were asked to rate their incisional pain using a 0–10 verbal rating scale, with 0 and 10 being no pain and the worst pain imaginable, respectively. The incidence of nausea or vomiting during the first 1 h after extubation was also recorded, and antiemetics (e.g. metoclopramide 10 mg i.v.) were administered as necessary. All patients were asked 24 h after operation if they had recall of intraoperative events.

STATISTICAL ANALYSIS

To evaluate the correlations between duration of anaesthesia and each emergence time, a regression line was constructed by the least squares method for each anaesthetic regimen. Because no significant correlation was found for the xenon and nitrous oxide–sevoflurane groups, they were compared with respect to each emergence time using an unpaired *t* test. Data (except duration of anaesthesia, pain rating, extradural analgesia level and incidence of nausea/vomiting) are reported as mean (SD) and were analysed using analysis of variance (ANOVA) followed by Dunnett's *t* tests with the xenon group as a control. The incidence of postoperative nausea/vomiting was analysed using a chi-square test. The remainder are expressed as median (range) and were analysed using the Kruskal–Wallis test with Mann–Whitney *U* tests used to assess differences between the xenon and other groups. $P<0.05$ was considered statistically significant.

Results

The three groups were comparable in age, height and weight (table 1). Duration of anaesthesia after the start of xenon or nitrous oxide anaesthesia was 58–380 min and did not differ between groups (table 1).

The rates of recovery from xenon and nitrous oxide–sevoflurane anaesthesia to four different end-points did not correlate with duration of anaesthesia, whereas those from nitrous oxide–isoflurane anaesthesia did (fig. 1A–D). Mean emergence times from xenon *vs* nitrous oxide–sevoflurane were: 3.3 (1.0) *vs* 5.6 (1.4) min to opening eyes; 3.6 (1.0) *vs* 6.3 (1.0)

Table 1 Patient data (mean (SD or range) or median[range])

	Xenon	N_2O–sevoflurane	N_2O–sevoflurane
Age (yr)	44 (33–58)	45 (32–64)	43 (34–56)
Height (cm)	158 (7)	156 (7)	157 (8)
Weight (kg)	58 (7)	56 (8)	56 (10)
No. of males	3	2	2
Duration of anaesthesia (min)	162 [58–380]	144 [58–303]	127 [61–296]

Table 2 Postoperative data. End-tidal carbon dioxide concentrations (E'_{CO_2}), ventilatory frequency and oesophageal temperature (temp.) were measured at the end of operation. Extradural dose=total volume of 1.5% mepivacaine with adrenaline 1:200 000 administered extradurally until 15 min after extubation. Pain rating=numerical quantification of incisional pain by the patient using a 0–10 verbal rating scale, with 0 and 10 being no pain and worst pain imaginable, respectively. Data are reported as mean (SD) or median [range]

	Xenon	N_2O–sevoflurane	N_2O–sevoflurane
E'_{CO_2} (kPa)	5.6 (0.5)	5.6 (0.7)	5.9 (0.5)
Ventilatory frequency (bpm)	21 (4)	23 (5)	20 (5)
Oesophageal temp (°C)	36.0 (0.2)	35.8 (0.2)	35.9 (0.3)
Extradural mepivacaine dose (ml)	36 (16)	32 (13)	31 (14)
Extradural analgesia level	T8 [T6–10]	T9 [T6–10]	T9 [T7–11]
Pain rating	3 [0–5]	2 [0–4]	2 [0–5]
Nausea/vomiting	9	7	6

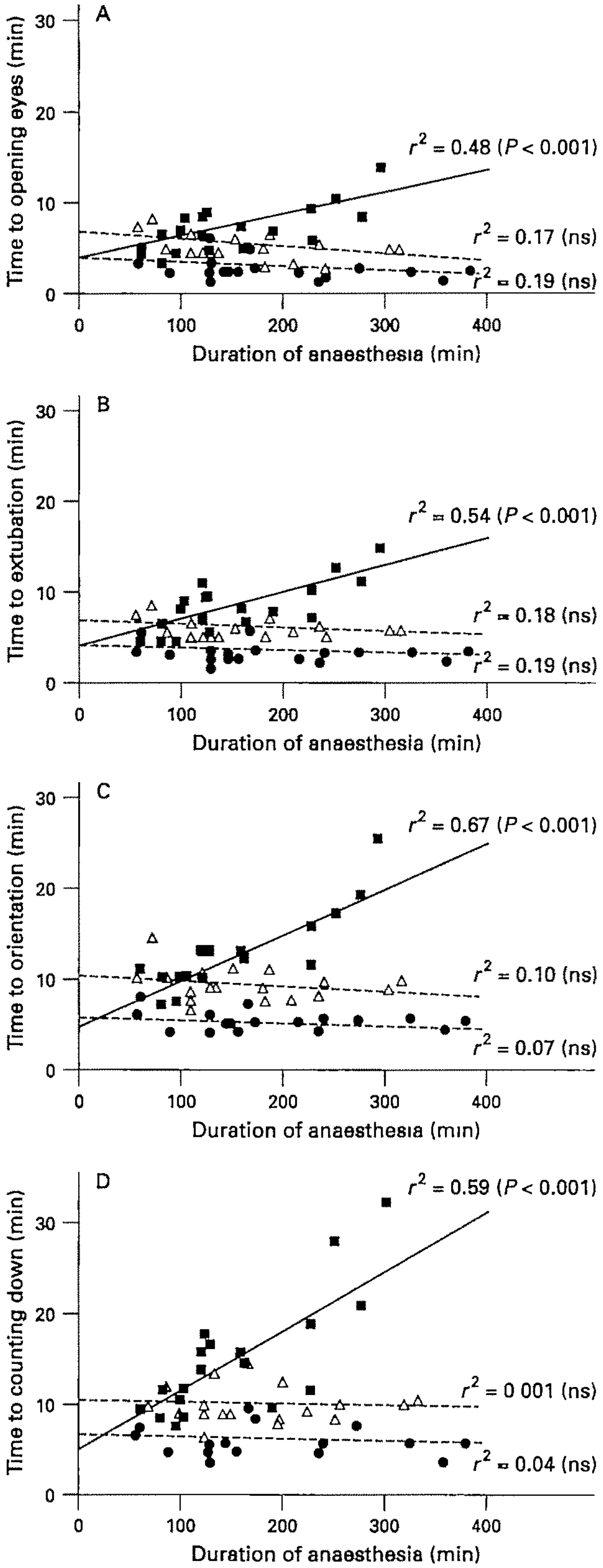

Figure 1 Correlations between duration of anaesthesia and emergence times from anaesthesia after xenon (●), nitrous oxide–sevoflurane (△) or nitrous oxide–isoflurane anaethesia (■) to four different end-points: from discontinuation of anaesthetic until patients could (A) open their eyes, (B) had their tracheas extubated, (C) state their name, date of birth and name of the hospital correctly (orientation), and (D) count backwards from 10 to 1 in less than 15 s. Each regression line was constructed by the least squares method. Whereas emergence times from nitrous oxide–isoflurane were correlated linearly with duration of anaesthesia ($P<0.001$), there was no significant correlation for xenon and nitrous oxide–sevoflurane, indicated by the broken regression lines.

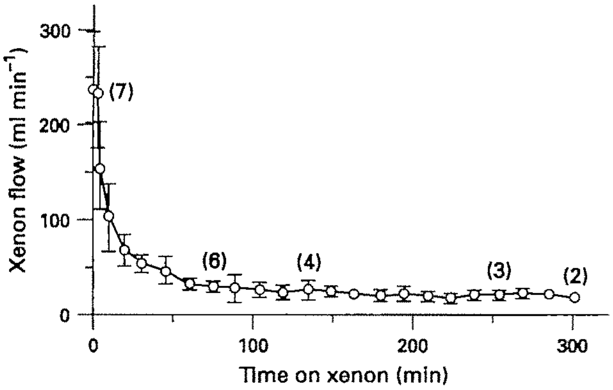

Figure 2 Inflow rate of xenon during closed-circuit anaesthesia. Data are mean (SD) for the number of patients indicated (parentheses). The least squares method revealed that (xenon inflow in ml min^{-1})$^{-1}$=0.005((time on xenon in min)$^{1/2}$ -1), r^2=0.75 (P<0.001).

min to tracheal extubation; 5.0 (1.1) *vs* 9.3 (1.8) min to regaining orientation; and 6.2 (1.7) *vs* 10.5 (2.0) min to counting down (all P<0.01).

The final end-tidal concentration of isoflurane in the xenon group was 0.1%. There was no difference in postoperative oesophageal temperature, E'_{CO_2}, ventilatory frequency, extradural analgesia level, pain rating or total amount of extradural mepivacaine administered (table 2). The incidence of postoperative nausea or vomiting was also comparable between groups (table 2). No subject experienced intraoperative awareness or other major anaesthesia-related adverse events.

The inflow rate of xenon after the system was closed declined exponentially from 229 (57) ml min^{-1} at 3 min to 33 (5) ml min^{-1} at 60 min and to <30 ml min^{-1} after 120 min (fig. 2). Expenditure of xenon between 3–60, 60–120, 120–180 and 180–240 min was 3819 (420) ml (n=7), 1721 (537) ml (n=6), 1358 (350) ml (n=4) and 943 (300) ml (n=4), respectively, excluding gas used to flush the anaesthesia system.

Discussion

We have demonstrated that xenon was associated with fast emergence from anaesthesia, regardless of duration. This was also the case with nitrous oxide–sevoflurane, although emergence times were approximately twice as long as those after xenon. In contrast, duration of anaesthesia had a significant impact on recovery from nitrous oxide–isoflurane. It was prolonged markedly after a long anaesthetic but was only slightly slower than that after xenon with a brief anaesthetic. The results are consistent with the widely accepted concept that lower blood:gas partition coefficients render emergence less dependent on duration of anaesthesia because of less accumulation of anaesthetic in body tissues.[5] This concept, however, assumes that the MAC fractions required to achieve each end-point of emergence are similar for different anaesthetics, although this assumption has been questioned recently[8] and xenon has never been compared with other agents in this regard. Other factors potentially influencing the rate of emergence such as age, sex, body temperature, pain and amount of supplementary anaesthetics and analgesics administered (including extradural local anaesthetic) did not differ between the three anaesthetic groups. Minute ventilation was also probably comparable because the end-tidal carbon dioxide concentration and ventilatory frequency at the end of operation were similar.

Our results also suggest that the quality of emergence after prolonged anaesthetics might be different between xenon and other inhalation agents, especially nitrous oxide–isoflurane. For example, when anaesthetics lasting more than 3 h are considered, all six patients who received xenon were oriented and able to count backwards by 5 and 8 min, respectively, whereas four of six patients anaesthetized with nitrous oxide–isoflurane were unable to open their eyes by 8 min. In accordance with this, patients in the xenon group in general appeared less sedated and more clear-headed in the post-anaesthesia period. Although it remains to be determined whether or not these characteristics lead to earlier "ward-readiness", xenon appears to have significant clinical potential in the setting where rapid, clear emergence is important.

The inflow rate of xenon required to conduct closed-circuit anaesthesia, which theoretically equals uptake by a patient, declined exponentially with time and followed a similar temporal pattern as those of other inhalation anaesthetics.[9] This has profound economical implications when expensive agents such as xenon are used, because the mean hourly expenditure, and hence cost, would be progressively lower with more prolonged anaesthetics. In this study, 2-, 3- and 4-h anaesthetics required approximately 10, 11.4, and 12.3 litre of xenon, including that used to initially increase the end-tidal concentration to 60%. The respective acquisition costs were approximately UK£80.00, £91.20 and £98.4, respectively (xenon costs UK£8.00 per litre in Japan). In comparison, nitrous oxide–isoflurane and nitrous oxide–sevoflurane anaesthesia with a total inflow of 3 litre min^{-1} cost UK£28.50 and £30.00 for 2 h, £42.75 and £45.00 for 3 h, and £57.00 and £60.00 for 4 h, respectively. (The prices of isoflurane and sevoflurane in Japan are the same, UK£0.50 per ml of liquid agent. Nitrous oxide costs UK£0.10 per litre of gas.) Thus the differences in cost between xenon and nitrous oxide–volatile anaesthetic combinations become smaller with a longer duration of administration. It could be reduced further by using the circuit priming method described elsewhere[10] instead of using high flow for the first 3 min as we did in this study. At the current price, however, xenon anaesthesia is still expensive. Whether or not the potential benefits of xenon, such as rapid recovery as demonstrated in this study, are sufficient to merit the increased costs remains to be determined.

In summary, we have demonstrated that xenon was associated with rapid emergence from anaesthesia, regardless of duration, which is consistent with its low blood:gas partition coefficient. In addition, uptake rate declined exponentially over time to less than 30 ml min^{-1} after 2 h of anaesthesia. These properties, together with its inert nature predicting low toxicity, would make xenon a favourable choice for prolonged anaesthesia. Further evaluation of its clinical characteristics and a cost–benefit ratio are warranted to determine if this "close-to-ideal" anaesthetic gas[11] can be adopted in clinical practice.

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Effect of systemic N-methyl-D-aspartate receptor antagonist (dextromethorphan) on primary and secondary hyperalgesia in humans

S. ILKJÆR, J. DIRKS, J. BRENNUM, M. WERNBERG AND J. B. DAHL

Summary

Dextromethorphan is a non-competitive N-methyl-D-aspartate (NMDA) receptor antagonist known to inhibit wind-up and central hyperexcitability of dorsal horn neurones. We studied 24 healthy, unmedicated male volunteers, aged 21–28 yr, in a randomized, double-blind, placebo-controlled, crossover study. Burn injuries were produced on the medial surface of the dominant calf with a 25×50 mm rectangular thermode. On three separate days, at least 1 week apart, subjects were given oral dextromethorphan 60 mg, 120 mg or placebo. Dextromethorphan reduced the magnitude of secondary hyperalgesia to pinprick but not to stroke. Dextromethorphan had no influence on primary hyperalgesia, pain during prolonged noxious heat stimulation or heat pain detection thresholds in undamaged skin. Side effects were frequent but clinically acceptable. The effects of dextromethorphan were in agreement with experimental studies indicating that dextromethorphan is a NMDA receptor antagonist. The effects of dextromethorphan in the burn injury model were similar to those of ketamine and distinct from those of local anaesthetics and opioids. (*Br. J. Anaesth.* 1997; **79**: 600–605).

Key words
Pharmacology, dextromethorphan. Pain, mechanism. Pain, postoperative. Model, burn injury.

Over the past several years, evidence has accumulated that peripheral tissue injury may lead to hyperexcitability of wide dynamic range (WDR) neurones in the dorsal horn. Prolonged C-afferent activity evokes wind-up, a state that results in increased receptive fields and exaggerated responses of the WDR neurones to afferent input.[1] Wind-up can augment responses of dorsal horn neurones up to 20-fold in magnitude and duration. This state of hyperexcitability may even continue after cessation of the peripheral input.[2] Central sensitization induces altered processing of afferent activity evoked by both innocuous and noxious stimuli. Clinically this is manifested as allodynia (pain caused by a stimulus that does not normally provoke pain) and hyperalgesia (increased response to a stimulus that is normally painful).[3] Injury-induced sensitization of dorsal horn neurones has been implicated as an important contributor to both acute and chronic pain states.[4]

Experimental studies have indicated that the N-methyl-D-aspartate (NMDA) receptor plays a significant role in wind-up and spinal hyperexcitability.[5 6] Both animal and human studies have shown that NMDA antagonists can reduce spinal hyperexcitability, leading to renewed interest in NMDA receptor antagonists such as ketamine and dextromethorphan.[7–11]

Dextromethorphan has been used as an antitussive agent for more than 30 yr. Since its development, little attention has been directed towards the CNS pharmacology of this drug. The discovery of high affinity binding sites for dextromethorphan in the brain and possible anticonvulsant, neuroprotectant, anti-ischaemic and anti-pain properties has lead to an increased interest in the drug.[12] Both dextromethorphan and its metabolite dextrorphan appear to be NMDA receptor antagonists.[13 14] Experimental studies indicated that dextromethorphan reduced NMDA-mediated nociceptive responses in the dorsal horn neurones[13–15] and a reduction in wind-up has been indicated in a clinical study.[10] It has been reported that the side effects of dextromethorphan are rare and mostly unimportant, and that the drug has a wide margin of safety.[16]

Cutaneous heat injury evokes allodynia and hyperalgesia for mechanical and heat stimuli within the injured area (primary hyperalgesia) and allodynia for mechanical, but not heat, stimuli in an area surrounding the injury (secondary hyperalgesia).[17] There is convincing evidence that secondary hyperalgesia is a result of altered central processing of afferent activity because of sensitization of dorsal horn neurones, whereas primary hyperalgesia seems to be caused by a combination of sensitization of

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SUSANNE ILKJÆR, MD, MOGENS WERNBERG, MD, Department of Anaesthesiology, Skejby Hospital, Aarhus University Hospital, DK-8200 Aarhus, Denmark. JESPER DIRKS, MD, JØRGEN B. DAHL, MD, PHD, Department of Anaesthesiology, Herlev University Hospital, DK-2730 Herlev, Denmark. JANNICK BRENNUM, MD, PHD, Department of Neurosurgery, Rigshospitalet, DK-2100 Copenhagen, Denmark. Accepted for publication: June 14, 1997.

Correspondence to S. I.

peripheral receptors and central neurones.[9 18–22] The burn injury model has been used previously to study the effects of various analgesics in human volunteers.[9 23 24]

The aim of the study was to investigate the effects of oral dextromethorphan on pain and hyperalgesia after a burn injury in human volunteers.

Subjects and methods

We studied 25 healthy, unmedicated male volunteers, mean age 24 (21–28) yr, after obtaining informed consent and approval from the regional Ethics Committee and the Danish National Health Board. One subject was excluded because of incorrect medication on one examination day. The study was performed in a quiet room with subjects in a semi-supine position. Each subject had been familiarized with the burn injury and measurement procedures on a separate day.

HYPERALGESIA

Burn injuries were produced on the medial surface of the dominant calf (L3–4 dermatome) with a 25×50 mm rectangular thermode (Thermotest, Somedic A/B Sweden) applied to the skin with a standardized pressure (8 kPa). The temperature of the thermode was 47 °C and application time was 7 min. This resulted in a first-degree burn injury, that is redness without blistering.

Pain ratings were performed continuously by the volunteer by moving a lever that controlled a vertical bar on a computer screen (sample rate 2 Hz). The visual analogue score (VAS) was anchored with the descriptors "no pain" (numerical value=0) and "worst possible pain" (numerical value=100). The interpretation of "pain" was left to the subject, who was instructed to apply the same interpretation throughout the study.

Brief conditioning was produced with the same thermode placed on the centre of the anterior side of the thigh at 45 °C.[9] After 3 min of heating, the border of hyperalgesia to pinprick and stroke stimuli was determined along four linear paths arranged radially around the thermal injury (see below). Immediately after these determinations the thermode was removed. These brief conditioning stimuli induced slight or no pain during heating and no spontaneous sensations after termination. The mechanical hyperalgesia induced by these brief conditioning stimuli never lasted more than a few minutes beyond the duration of the conditioning stimuli.

MEASUREMENT OF MECHANICAL HYPERALGESIA

The temperature of the injured site was stabilized at 35 °C, with the above described thermode, from 1 min before and throughout assessment of mechanical hyperalgesia. The border of hyperalgesia to pinprick and stroke stimuli was determined by stimulating along four linear paths arranged radially around the thermal injury in steps of 5 mm at intervals of 1 s, starting well outside the hyperalgesic area where neither stimulus type evoked pain. Stimulations continued towards the injury until subjects reported a clear change in sensations ("burning", "tenderness", "more intense pricking"). The areas of hyperalgesia were calculated using a vector algorithm.[23] Pinprick was performed with the von Frey technique using a nylon filament with a diameter of 1 mm and a bending force of 1.15 N. Stroke stimulation was performed by lightly stroking the skin with a gauze swab.

MEASUREMENT OF THERMAL THRESHOLDS

Heat pain detection threshold (HPDT) was defined as the lowest temperature percived as painful. The thermode was identical to that used for production of the burn injury. HPDT was determined from a baseline temperature of 32 °C with a rate of change of 1 °C s^{-1}. By pressing a button, subjects indicated when the pertinent threshold was reached. This value was recorded and the stimulator returned to baseline. If the cut-off limit (52 °C) was reached before the pertinent threshold, the thermode returned automatically to baseline and a threshold of 52 °C was registrered (it did not happen in any of the threshold measurements). Each threshold was calculated as the average of three measurements with randomized intervals (6–10 s) between each stimulation. Thermal thresholds were determined at the site of injury and at the corresponding site of the contralateral, unburned calf.

Table 1 Experimental design

Time	Actions/measurements
Baselines	Area of secondary hyperalgesia to pinprick and stroke during brief conditioning, thigh.
	Heat pain detection threshold (HPDT), right and left calf
0 min	Oral dextromethorphan 60 mg, 120 mg or placebo
105–115 min	Side effects
	Area of secondary hyperalgesia to pinprick and stroke during brief conditioning, thigh
	HPDT, right and left calf
120–127 min	Burn injury, right calf; measurement of pain with electronic VAS during burn
180–200 min	Side effects
	Area of secondary hyperalgesia to pinprick and stroke during brief conditioning, thigh
	HPDT, right and left calf
	Area of secondary hyperalgesia to pinprick and stroke around burn injury, right calf
240–260 min	Side effects
	Area of secondary hyperalgesia to pinprick and stroke during brief conditioning, thigh
	HPDT, right and left calf
	Area of secondary hyperalgesia to pin prick and stroke around burn injury, right calf

ASSESSMENT OF SIDE EFFECTS

Drowsiness was assessed on an 11-point analogue scale (0=completely awake; 10=almost asleep). Discomfort was assessed on an 11-point analogue scale (0=no discomfort; 10=maximum discomfort). Dizziness was assesed on an 11-point analogue scale (0=no dizziness, 10=maximum dizziness). Nausea was registered as four graduations (none, light, moderate or severe). Finally, subjects were asked if they experienced other sensations.

EXPERIMENTAL PROCEDURE

On three separate days, at least 1 week apart, subjects received oral dextromethorphan 60 mg, 120 mg or placebo, 2 h before induction of hyperalgesia. The study was double-blind and the order of treatments was randomized. Timing of the various assessments is shown in table 1.

STATISTICAL ANALYSIS

Data are presented as median (lower and upper quartiles). Variables were evaluated with Wilcoxon's test for paired data. All significant *P* values were corrected with Bonferroni's test for repeated measurements. $P<0.05$ was considered statistically significant.

Results

CONTROL (PLACEBO) DAY

Pain during burn injury increased rapidly during the first 15–30 s, reached a plateau and then remained relatively stable during the remaining 6 min (fig. 1).

After induction of injury, no spontaneous pain or other sensations were experienced from the site of injury.

The borders of secondary hyperalgesia for pinprick and stroke stimuli surrounding the burn injury on the calf (table 2) and the area of secondary hyperalgesia for pinprick and stroke stimuli evoked by brief conditioning on the thigh (table 3) were detected easily in all subjects.

HPDT inside the burned area decreased from a baseline value of 47.6 (47.0–48.8) °C to 44.4 (43.6–45.8) °C, 60 min after the injury, and remained decreased throughout the study ($P<0.05$) (table 4). HPDT on the contralateral calf did not change throughout the study ($P>0.05$) (table 4).

EFFECTS OF DEXTROMETHORPHAN

There were no differences in pain ratings during

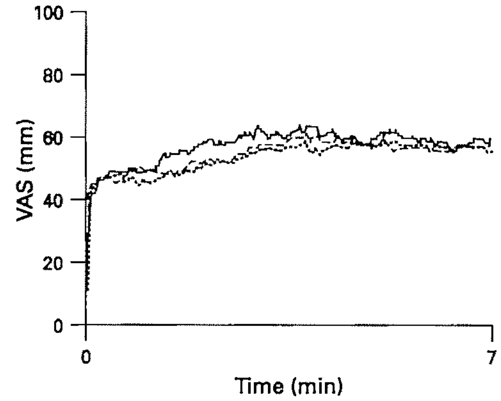

Figure 1 Median pain scores (VAS) during burn injury after treatment with dextromethorphan 120 mg (–), 60 mg (....) and placebo (–––) (ns, Wilcoxon rank test).

Table 2 Area of secondary hyperalgesia to pinprick and stroke stimuli (cm^2) around the burn injury during treatment with dextromethorphan 120 mg, 60 mg and placebo (medians (lower and upper quartiles)). *$P<0.05$ compared with placebo

	Dextromethorphan 120 mg	Dextromethorphan 60 mg	Placebo
Pinprick			
180 min	69 (43–82)*	67 (52–94)	78 (54–110)
240 min	60 (49–84)	65 (43–110)	75 (54–104)
Stroke stimuli			
180 min	34 (21–55)	37 (27–48)	41 (25–77)
240 min	35 (19–56)	38 (24–57)	35 (21–59)
after oral dextromethorphan			

Table 3 Area of secondary hyperalgesia to pinprick and stroke stimuli induced by brief conditioning on the thigh during treatment with dextromethorphan 120 mg, 60 mg and placebo (medians (lower and upper quartiles)). *$P<0.05$ compared with placebo

	Dextromethorphan 120 mg	Dextromethorphan 60 mg	Placebo
Pinprick			
Baseline	97 (72–120)	89 (71–115)	109 (81–129)
105 min	93 (59–116)	93 (60–140)	96 (67–122)
180 min	71 (42–116)*	86 (57–133)	99 (70–117)
240 min	81 (46–115)	110 (64–141)	89 (73–131)
Stroke stimuli			
Baseline	54 (38–74)	63 (45–93)	52 (34–84)
105 min	50 (26–87)	67 (40–103)	52 (35–83)
180 min	47 (35–55)	57 (47–90)	59 (37–73)
240 min	47 (38–65)	67 (50–104)	59 (38–89)
after oral dextromethorphan			

Table 4 Heat pain detection thresholds (°C) on the unburned and burned calf during treatment with dextromethorphan 120 mg, 60 mg and placebo (medians (lower and upper quartiles))

	Dextromethorphan 120 mg	Dextromethorphan 60 mg	Placebo
Unburned calf			
Baseline	48.1 (46.7–49.5)	47.7 (46.6–49.2)	47.8 (46.6–48.9)
105 min	48.1 (47.3–48.9)	47.4 (46.4–48.2)	47 6 (46.5–48.4)
180 min	47.6 (46.3–48.2)	47.8 (46.5–48.8)	47 1 (46.2–47.9)
240 min	47.7 (46.7–49.1)	47.6 (46.5–49.0)	47.7 (46.8–48.4)
Burned calf			
Baseline	48.4 (47.1–50.1)	47.5 (46.5–49.1)	47.6 (47.0–48.8)
105 min	48.4 (47.3–49.4)	47.3 (46.2–48.7)	47 7 (46.8–48.9)
180 min	45.6 (43.1–47.1)	45.5 (42.3–47.0)	44.4 (43.6–45.8)
240 min	46.3 (43.5–47.5)	46.1 (44.0–47.0)	45.5 (44.5–47.5)
after oral dextromethorphan			

induction of the burn injury between dextromethorphan 120 mg, 60 mg or placebo (fig. 1) (120 mg *vs* placebo, $P=0.60$; 60 mg *vs* placebo, $P=0.98$ (Wilcoxon rank test)).

MEASUREMENT OF MECHANICAL HYPERALGESIA

At the burn injury (calf) the areas of secondary hyperalgesia to pinprick but not to stroke were reduced by dextromethorphan 120 mg compared with placebo at 180 min after administration of the drug ($P<0.008$, corrected for multiple comparisons (pinprick), $P=0.07$ (stroke)). There was no difference in the areas at 240 min ($P=0.10$ (pinprick), $P=0.74$ (stroke)) (table 2).

Dextromethorphan 60 mg had no influence on the area of secondary hyperalgesia for pinprick ($P=0.24$, $P=0.51$) or for stroke ($P=0.29$, $P=0.08$) at 180 min or 240 min after administration of the drug, respectively (table 2).

On the thigh, the area of secondary hyperalgesia to pinprick but not to stroke was reduced by dextromethorphan 120 mg compared with placebo at 180 min but not at 240 min after drug administration ($P=0.048$, corrected for multiple comparisons). No significant effects were observed with dextromethorphan 60 mg (table 3).

MEASUREMENT OF THERMAL THRESHOLDS

At the site of injury there was no difference in the decrease in HPDT between dextromethorphan 120 mg, dextromethorphan 60 mg or placebo treatment (dextromethorphan 120 mg *vs* placebo, $P>0.1$; dextromethorphan 60 mg *vs* placebo, $P>0.2$). Hence, dextromethorphan in these doses did not influence primary hyperalgesia (table 4).

At the contralateral uninjured calf there was no difference in HPDT between dextromethorphan 120 mg, dextromethorphan 60 mg or placebo treatment (dextromethorphan 120 mg *vs* placebo, $P>0.07$; dextromethorphan 60 mg *vs* placebo, $P>0.1$). Hence dextromethorphan had no influence on HPDT in non-injured skin (table 4).

SIDE EFFECTS

Dizziness was more pronounced with dextromethorphan 120 mg, but not with 60 mg, compared with placebo ($P<0.05$) (range 1–5 on the analogue scale). The difference was significant at 105 and 180 min, but not at 240 min after administration. Only a few subjects experienced slight nausea, drowsiness and discomfort, but these adverse effects were observed also in the placebo group. In general, the frequency of side effects was low, and after 240 min they had almost disappeared. No volunteer wished to leave or was excluded from the study because of side effects. All volunteers were able to collaborate fully during the various assessments without problems.

Discussion

In this study we found dextromethorphan to have a slight but statistically significant inhibitory effect on mechanical allodynia for pinprick in the area of secondary hyperalgesia after a burn injury in humans. There was no effect on heat pain detection thresholds in normal or injured skin, on mechanical allodynia for stroke in the area of secondary hyperalgesia or on pain evoked by prolonged heat stimuli.

NMDA receptor antagonists differ from "classic" analgesics in their mechanisms of action. They have no effect on the initial nociceptive input, as do opioids or local anaesthetics, but they reduce wind-up and injury-induced facilitation of nociceptive neurones in the CNS. Thus these drugs are expected to exert their analgesic effects only under conditions where tissue damage (e.g. burn injury) or repetitive C-fibre stimulation has induced hyperexcitability of dorsal horn neurones.[2]

Experimental studies have shown that dextromethorphan can reduce wind-up,[13] formalin-induced increases in spinal cord *c-fos* mRNA[15] and pain behaviour.[14 15] Furthermore, dextromethorphan attenuates analgesic tolerance to morphine,[25 26] and it possesses additive analgesic effects when combined with NSAID.[27]

Human studies on dextromethorphan and pain have shown controversial results.[10 11 28–30] In a double-blind, randomized, placebo-controlled crossover design where six volunteers were given oral doses of dextromethorphan 15, 30 or 45 mg, or placebo, Price and colleagues found that dextromethorphan reduced slow temporal summation of electrically and thermally evoked second pain (a correlate with wind-up) in a dose-dependent manner.[10] In another study, oral dextromethorphan 100 and 200 mg did not attenuate pain produced by topical capsaicin or ischaemia 45 min after oral administration, but side effects were pronounced with the higher dose.[30] Wind-up, hyperalgesia or other correlates with central neuronal alterations were not evaluated specifically.[30] Thus it is uncertain if central hyperexcitability had been induced or if effective plasma concentrations were achieved at the time of assessment.[30]

One preliminary clinical study has evaluated the analgesic effect of dextromethorphan after oral surgery. Doses of 60 and 120 mg were given before and every 6 h after operation, and pain was evaluated for 48 h after surgery. Dextromethorphan produced a weak analgesic effect 6 h after operation.[28] Furthermore, in a double-blind, randomized, crossover study, small doses of dextromethorphan (13.5 and 27 mg three times a day) had no effect on neuropathic pain.[29]

Dextromethorphan 60 or 90 mg qid or up to 10 mg kg^{-1} day^{-1}, with total doses in the range 4.8–10 mg kg^{-1} day^{-1}, respectively, have been administered to patients with either a history of transient ischaemic attacks or with amyotrophic lateral sclerosis, with minor but dose-limiting side effects.[31 32]

In this study doses of oral dextromethorphan 60 and 120 mg were chosen because of the lack of analgesic effect with smaller doses in a previous clinical study,[29] the relatively minor side effects observed with higher doses in neurological patients[31 32] and the unacceptable side effects observed with 200 mg in a study in human volunteers.[30] The burn injury was induced 2 h after administration of dextromethorphan as plasma concentrations have been found to be at their maximum 2 h (range 1–4 h) after oral intake.[32] Dextromethorphan reduced secondary hyperalgesia surrounding a first-degree burn injury, and secondary hyperalgesia during short lasting thermal conditioning of the skin. These findings, together with the lack of effect on heat pain detection thresholds in unburned skin, are consistent with previous experimental results[13 15] and with the observations of Price and colleagues.[10] They confirmed that dextromethorphan may reduce injury-induced alterations in dorsal horn neurones without any effect on nociceptive input *per se*. The reduction was significant for pinprick but not for stroke hyperalgesia 3 h after administration of the drug. Taking the side effects into account this could be the period with the highest plasma concentration of the drug; 4 h after drug administration, side effects were reduced and the reduction in secondary hyperalgesia compared with placebo had disappeared.

Cervero and colleagues examined the appearance of secondary hyperalgesia to pinprick and stroke after non-painful heat stimuli.[33] They found that the area of pinprick developed first, followed by flare and hyperalgesia for stroke. This indicates that hyperalgesia to pinprick and stroke may be mediated by different mechanisms.[33] In a recent study, ketamine reduced hyperalgesia for both pinprick and stroke because of a burn injury,[9] while in another study capsaicin-induced hyperalgesia for pinprick, but not for stroke, was reduced by ketamine.[11] This indicates that secondary hyperalgesia for punctuate stimuli are attenuated more by NMDA antagonists than secondary hyperalgesia for stroke. Pain during induction of the burn injury, and heat pain detection thresholds in burned skin, were not influenced by dextromethorphan in contrast with the findings for ketamine.[9] One explanation for this discrepancy could be that in our study dextromethorphan had not reached an adequate plasma concentration during induction of the burn injury but may also reveal differences in potency or mechanisms of action between the two drugs.

Although dextromethorphan induced (insignificant) drowsiness at both doses, heat pain detection thresholds in both healthy and injured skin were unaffected by dextromethorphan. This indicates that the reduction in secondary hyperalgesia with dextromethorphan 120 mg was not caused by side effects.

Our study is in accordance with previous findings and confirms that dextromethorphan may reduce injury-induced alterations in dorsal horn neurones without any effect on nociceptive input *per se*. In experimental studies the combination of NSAID and dextromethorphan was found to have additive analgesic effects and the combination with morphine reduced the development of tolerance.[25–27] Human studies have not yet been performed. Our study provides a rationale for further studies of the effects of dextromethorphan in combination with other analgesics on clinical pain states, such as postoperative pain.

Acknowledgements

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Comparison of perioperative ketoprofen 2.0 mg kg^{-1} with 0.5 mg kg^{-1} i.v. in small children during adenoidectomy

E. NIKANNE, H. KOKKI AND K. TUOVINEN

Summary

We have investigated if ketoprofen 0.5 mg kg^{-1} i.v. provided as good analgesia with less adverse effects compared with ketoprofen 2.0 mg kg^{-1} i.v. in 107 children, aged 1–7 yr, after adenoidectomy, in a randomized, double-blind, parallel group study design. A standard anaesthetic method was used and all children received fentanyl 1 μg kg^{-1} i.v. during induction. Children in group 2.0 received ketoprofen 2.0 mg kg^{-1} and children in group 0.5, 0.5 mg kg^{-1} i.v. during induction. If the child was in pain, fentanyl 1 μg kg^{-1} was given i.v. as rescue analgesia. We found that ketoprofen provided good analgesia and only 49% of children required fentanyl in the post-anaesthesia care unit. There were no differences between the groups in the number of fentanyl doses, pain scores or frequency of adverse reactions. No serious adverse reactions occurred. (*Br. J. Anaesth.* 1997; **79**: 606–608).

Key words
Analgesia, pre-emptive. Analgesics non-opioid, ketoprofen. Children. Anaesthesia, day-case. Surgery, otolaryngological.

Postoperative pain is frequent in children, even after minor surgery. After myringotomy alone, more than 40%[1] and after adenoidectomy at least 80% of children need analgesic treatment.[2]

Adenoidectomy is performed frequently as a day-case operation and in most cases the patients are small children. It is important to find an effective and safe analgesic treatment for these patients. Opioids have been used because of their good analgesic effects, although adverse effects include emesis, excessive sedation and the risk of respiratory depression.

Non-steroidal anti-inflammatory drugs (NSAID) have been used for pain treatment in day-case surgery for mild and moderate pain and as a background analgesic for severe pain with good results.[3] They also have known adverse effects such as gastrointestinal and renal dysfunction. NSAID increase perioperative bleeding by inhibiting cyclo-oxygenase and this leads to a prolonged bleeding time by inhibition of platelet thromboxane A_2 production and platelet aggregation. Inhibition of cyclo-oxygenase depends on the blood concentration of the drug.[4] Because these adverse effects are dose dependent it is important to find the smallest effective dose of the drug.

Ketoprofen is a NSAID with the chemical composition of 2-(3-benzophenyl)-propionic acid.[5] It is available in i.v., i.m., oral and rectal formulations. In our previous study we showed that perioperative i.v. ketoprofen had a good analgesic effect in a dose of 2 mg kg^{-1} during adenoidectomy.[6] Ketoprofen has been recommended for administration in a dose of 2.5 mg kg^{-1} for acute pain in children.[4] In an oral dose of 0.5 mg kg^{-1}, ketoprofen has been shown to have a good antipyretic effect.[7]

The aim of this study was to see if ketoprofen 0.5 mg kg^{-1} i.v. provided as good analgesia with less adverse effects compared with ketoprofen 2.0 mg kg^{-1} i.v. in children aged 1–7 yr after adenoidectomy.

Patients and methods

The study was approved by the Ethics Committee of Kuopio University Hospital and the parents of patients gave written informed consent. We studied 107 ASA I patients, aged 1–7 yr, undergoing adenoidectomy. Patients were excluded if they had a known allergy to ketoprofen or other NSAID, asthma, kidney or liver dysfunction, or haemorrhagic diathesis. A randomized, double-blind, parallel group study design was used. Children were allocated randomly to either group 2.0 (ketoprofen 2.0 mg kg^{-1}) ($n=54$) or group 0.5 (ketoprofen 0.5 mg kg^{-1}) ($n=53$).

A standard anaesthetic technique was used. Each child was premedicated with diazepam 0.5 mg kg^{-1} orally up to a maximum of 10 mg, 30–45 min before induction of anaesthesia. EMLA cream (Astra, Sweden) was applied to the skin 60 min before venepuncture. Anaesthesia was induced with thiopentone 5–7 mg kg^{-1} and fentanyl 1 μg kg^{-1} i.v. and tracheal intubation was facilitated with atracurium 0.5 mg kg^{-1}. All children received fentanyl 1 μg kg^{-1} i.v. at induction and no more opioid was given during operation.

ELINA NIKANNE, MD (Department of Otorhinolaryngology); HANNU KOKKI, MD (Department of Anaesthesiology and Intensive Care); KATI TUOVINEN, MSC (PHARM) (Department of Pharmacy); Kuopio University Hospital, PO Box 1777, FIN-70211 Kuopio, Finland. Accepted for publication: June 9, 1997.
Correspondence to H. K.

After induction of anaesthesia, children received ketoprofen (Orudis, Rhone-Poulenc-Rorer, Denmark) 2.0 or 0.5 mg kg^{-1} dissolved in 10 ml of 0.9% saline injected i.v. over 10 min. Anaesthesia was maintained with 1–1.2% isoflurane (inspired concentration) and 65% nitrous oxide in oxygen with IPPV. On completion of the procedure, neuromuscular block was antagonized with neostigmine 50 μg kg^{-1} and glycopyrronium 10 μg kg^{-1}.

All children were given 0.9% saline 10 ml kg^{-1} h^{-1} for intraoperative fluid maintenance. After surgery, children were transferred to the post-anaesthesia care unit (PACU) for continuous monitoring of vital signs and assessment of pain.

The adenoids were removed using indirect currettizarion. Haemostasis was controlled with nasopharyngeal packs with or without electrocautery. Surgeons estimated the amount of bleeding using a five-point scale (1="no bleeding", 2="less than normal", 3="normal", 4="more than normal" and 5="profuse").

Postoperative pain was assessed by the Maunuksela score,[8] which is an observer assessment based on facial expression, vocalization, movement or rigidity of the limbs and body, response to handling and irritability, together with measured cardiorespiratory variables. In the modified score, 0="no pain", 1–3="mild pain", 4–6="moderate pain", 7–9="severe pain" and 10="worst possible pain".

Specially trained research nurses assessed the pain expressed by the child at rest and during swallowing. If the child was in pain (pain score at rest was 3 or more) fentanyl 1 μg kg^{-1} was given i.v. for rescue analgesia. The dose was repeated at 5-min intervals until the child was comfortable. No more than three doses of fentanyl were allowed in 1 h. No other analgesic medication was permitted during the study. The children were monitored closely after each dose of fentanyl in the PACU. On leaving hospital, pain was assessed by a specially trained research nurse at rest and during swallowing. All adverse reactions were recorded and summarized for each patient.

Analysis of variables was performed using the two tailed Student's *t*-test and chi-square test. $P<0.05$ was considered statistically significant. Results are presented as number of patients (%) or mean (SD) where appropriate.

Results

Sex distribution, age, weight and type of surgery performed were similar in the two groups (table 1).

There were no differences in the number of fentanyl doses needed in the PACU. In group 2.0, 27 (50%) and in the group 0.5, 25 (47%) children needed supplementary doses of fentanyl. The number of fentanyl doses needed in the PACU was 0.7 (SD 0.8) in both groups.

There were no differences between the groups in the Maunuksela pain scores (table 2).

In the PACU there was no difference in the frequency of adverse reactions between the groups (table 3). In group 2.0, seven (13%) and in the group 0.5, nine (17%) children had one or more adverse reactions. There were no serious adverse reactions but one patient who received ketoprofen 2.0 mg kg^{-1} developed minor urticaria and conjunctivitis.

Table 1 Patient data for the two groups (mean (SD or range) or number)

	Group 2.0 (n=54)	Group 0.5 (n=53)
Sex (M/F)	29/25	34/19
Weight (kg)	15 (5)	16 (5)
Height (cm)	95 (15)	99 (16)
Age (months)	37 (12–91)	42 (14–88)

Table 2 Maunuksela pain scores in the post-anaesthesia care unit (PACU) (mean (SD))

	Group 2.0 (n=54)	Group 0.5 (n=53)
After 1 h		
At rest	1.9 (2.7)	1.8 (2.4)
Swallowing	2.7(3.2)	2.3 (2.7)
After 2 h		
At rest	1.0 (2.0)	1.2 (2.1)
Swallowing	1.3 (2.3)	1.4 (2.2)
On leaving the PACU		
At rest	0.2 (0.8)	0.1 (0.4)
Swallowing	0.2 (0.8)	0.2 (0.5)
Worst pain in the PACU		
At rest	2.5 (2.9)	2.4 (2.6)
Swallowing	3.1 (2.9)	2.8 (2.9)

Table 3 Number of adverse reactions in the post-anaesthesia care unit (n (%)). One child in group 2.0 required overnight admission because of an allergic reaction. * P=0.56 (chi-square test)

	Group 2.0 (n=54)	Group 0.5 (n=53)
Nausea and/or vomiting	4 (7)	4 (8)
Sedated	—	3 (6)
Pain or redness at the puncture site	1 (2)	1 (2)
Sa_{O_2} <90	1 (2)	—
Postoperative bleeding	1 (2)	—
Allergic reaction	1 (2)	—
Headache	—	1 (2)
Difficulty in passing urine	—	1 (2)
Total No. of adverse reactions	8	10
No. of patients with one or more adverse reactions	7 (13)	9 (17)*
Mean (SD)	0.1 (0.3)	0.2 (0.4)

Table 4 Intraoperative bleeding estimated by the surgeon (n (%)). P=0.61 (chi-square test)

	Group 2.0 (n=54)	Group 0.5 (n=53)
Less than normal	7 (13)	4 (8)
Normal	38 (70)	41 (77)
More than normal	9 (17)	8 (15)

The surgeon estimated the amount of intraoperative bleeding using a five-point scale. There was no difference between the groups in the amount of bleeding (table 4). One child in group 2.0 had postoperative bleeding and was transferred to the ward. The bleeding stopped without any intervention. He was observed for a few hours before being discharged.

Discussion

We have found that i.v. ketoprofen at a dose 2.0 mg kg^{-1} did not provide better analgesia than a dose of 0.5 mg kg^{-1} in small children during adenoidectomy. The Maunuksela pain scores were at acceptable levels throughout the study in both groups.

In the PACU only 49% of all children needed supplementary doses of i.v. fentanyl and there was no difference between the groups in the need for supplementary analgesia. In 31% of patients, one dose and in 17% of patients, two doses of fentanyl were given. We found that the need for supplementary doses of fentanyl was smaller than expected, possibly because of the analgesic effects of i.v. ketoprofen during operation.

The incidence of adverse reactions was 15%. In previous studies on the use of ketoprofen the incidence varied from 0% to approximately 50% of patients.[5] There were no serious adverse effects in this study but one patient in group 2.0 had an allergic reaction after injection of ketoprofen and developed urticaria and conjunctivitis. The child was treated with an antihistamine, which alleviated his symptoms in a few hours, but he was observed in a ward overnight. The cause of this allergic reaction was possibly ketoprofen. On the other hand, atracurium is known to release histamine and this may have been a possible cause for the urticaria and conjunctivitis. The incidence and scale of adverse reactions in our study were comparable with other reports of short-term use of NSAID in children.[3 9]

Epigastric distress is a known adverse effect of NSAID but did not occur in this study. This may be because of the small dose of ketoprofen used and also because it was administered i.v. Oral ketoprofen may cause epigastric distress by local irritation of the gastric mucosa. In our previous study, one child in the ketoprofen group and one child in the placebo group experienced epigastric distress.[6]

Increased perioperative bleeding has been shown to occur with ketorolac 1 mg kg^{-1}.[10 11] Gunter and colleagues even suggested that ketorolac is contraindicated in children undergoing adenotonsillectomy.[11] In their study ketorolac was used in a dose of 1 mg kg^{-1}. In our opinion this dose is rather excessive because in a previous study a dose of 0.2 mg kg^{-1} had a good analgesic effect after major surgery in children.[9]

We found no difference between the groups in the amount of intraoperative bleeding and none of the children needed further treatment because of bleeding. Only one child in group 2.0 experienced postoperative bleeding. This child was observed for a few hours before discharge. In our previous study, intraoperative bleeding estimated by the surgeon proved to be greater if children received ketoprofen 1 mg kg^{-1} during operation instead of placebo.[6] In that study none of the children experienced bleeding which required intervention or delay in discharge from hospital.

In our opinion, based on this and our previous study,[6] i.v. ketoprofen is a useful analgesic in children undergoing day-case surgery. It provided good analgesia after adenoidectomy in children and we found no major problems with adverse effects or perioperative bleeding. In our two studies, only one of 271 children required an overnight stay in hospital and none needed treatment for bleeding.

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Knee–chest *vs* horizontal side position during induction of spinal anaesthesia in patients undergoing lumbar disc surgery

E. LAAKSO, M. PITKÄNEN, J. KYTTÄ AND P. H. ROSENBERG

Summary

In the prone knee–chest position the spread of plain 0.5% bupivacaine in the cerebrospinal fluid and associated haemodynamic changes may be different compared with the horizontal position. A randomized comparison was performed in 40 ASA I–II patients, aged 24–61 yr, undergoing lumbar disc surgery. Subarachnoid injection (27-gauge needle) at the L2–3 interspace with 3 ml of 0.5% bupivacaine was performed with the patient in the operative knee–chest position (prone knee–chest group, *n*=20) or in the horizontal side position (supine side horizontal group, *n*=20). Patients in the supine side horizontal group were turned into the horizontal supine position for 20 min, and subsequently they were placed in the operative knee–chest position. In three patients in the prone knee–chest group, the spinal needle was replaced by a larger needle (25-gauge). The final cephalad extension of sensory analgesia on skin tested by pinprick was T5 (median) in the prone knee–chest group and T6 in the supine side horizontal group. Recovery was also similar, on average 210 min from injection in both groups. The mean decrease in systolic arterial pressure was somewhat greater in the prone knee–chest group (30 mm Hg) than in the supine side horizontal group (13 mm Hg). The need for ephedrine occurred earlier in the supine side horizontal group (three patients, all within 10 min from local anaesthetic injection) than in the prone knee–chest group (six patients, all after 15 min). Four of the latter patients also required administration of an anticholinergic for bradycardia compared with two patients in the supine side horizontal group. Light sedation was given to five patients in the prone knee–chest group and to four in the supine side horizontal group because of numbness and aching in the shoulders. We conclude that spinal block was similar in the two groups but there was a tendency to more frequent episodes of haemodynamic deterioration in the knee–chest position. (*Br. J. Anaesth.* 1997; **79**: 609–611).

Key words

Anaesthetic techniques, subarachnoid. Surgery, spinal. Position, effects. Anaesthetics local, bupivacaine.

Although general anaesthesia is used more often than spinal anaesthesia, the latter is gaining popularity in microscope-assisted surgery of herniated lumbar discs.[1 2] Intrathecal puncture can be performed before positioning for surgery or with the patient in the prone knee–chest position.

The spread of spinal anaesthesia with the slightly hypobaric bupivacaine solution and associated haemodynamic changes may be different in the knee–chest position compared with the supine horizontal position. In addition, decreased venous flow in the lower extremities of patients in the knee–chest position[3] may predispose to lowering of cardiac output[4] and arterial pressure.

In this randomized study, we have compared spinal anaesthesia with plain bupivacaine performed in patients in the knee–chest and horizontal side positions during induction of block.

Patients and methods

The study was approved by the Ethics Committee of the hospital. After obtaining informed consent, we studied 40 patients, ASA I–II, aged 24–61 yr, undergoing primary lumbar disc surgery under spinal anaesthesia (table 1). All patients received diazepam 0.15–0.2 mg kg^{-1} orally as premedication, 45–60 min before anaesthesia. Clinical monitoring included ECG, non-invasive arterial pressure (oscillotonometer) and haemoglobin oxygen saturation ($S\mathrm{p}_{\mathrm{O}_2}$). Ringer's acetate 100–200 ml was given i.v. before local anaesthetic injection and then approximately 8 ml kg^{-1} in 20 min. Thereafter the infusion rate was reduced to 100–200 ml h^{-1}.

Patients were allocated randomized to one of two groups. In the prone knee–chest group, patients received the subarachnoid injection after first positioning themselves in the knee–chest position on the operation table. Because of this position and the small size of the spinal needle there was usually no free flow of cerebrospinal fluid (CSF) and hence the correct position of the needle tip was ascertained by aspirating CSF (0.2–0.3 ml) through the needle before injecting the anaesthetic. The table was then

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E. LAAKSO*, MD, M. PITKANEN, MD, PHD, J. KYTTÄ, MD, PHD, P. H. ROSENBERG, MD, PHD, Department of Anaesthesiology, Helsinki University Central Hospital, Toolo Hospital, FIN-00260 Helsinki, Finland. Accepted for publication. July 7, 1997

*Address for correspondence: Toolo Hospital, Topeliuksenkatu 5, 00260 Helsinki, Finland.

turned so that the "hip–shoulder joint" line was 20° head-up with respect to the horizontal line.

Patients in the supine side horizontal group received the subarachnoid local anaesthetic injection in the horizontal side position and were turned immediately into the supine position for 20 min. These patients were then placed in the knee–chest position with the assistance of personnel.

In both groups subarachnoid block was performed with a 27-gauge Quincke-type needle in the L2–3 interspace and 3.0 ml of 0.5% bupivacaine were injected. The level of spinal analgesia was tested by pinprick at 5, 10, 15, 20, 30, 45 and 60 min, and thereafter at 30-min intervals after the subarachnoid injection.

If systolic arterial pressure decreased by more than 25% from the preoperative value and the patient had clinical symptoms of arterial hypotension, or systolic arterial pressure decreased to less than 90 mm Hg, ephedrine 5 mg was given i.v. If heart rate decreased to >25% or less than 45 beat min^{-1}, atropine 0.5 mg was given i.v.

All comments by patients were recorded and patients were interviewed by one of the investigators on the next day. Patients left hospital on the second day after operation, or later, and they were asked to report any further symptoms possibly associated with anaesthesia.

For data analysis, descriptive statistics were used. For comparisons between groups, ANOVA and the Mann–Whitney *U* test were used, where appropriate. $P<0.05$ was considered statistically significant.

Results

Patients characteristics were comparable in the two groups (table 1). In three cases in the prone knee–chest group the 27-gauge needle was changed for a 25-gauge needle because of difficulties with identification of the subarachnoid space and multiple puncture attempts. There was no significant difference in the maximum median level of analgesia between the groups (fig. 1). The time to maximum spread (median dermatomal level) of analgesia was 45 min in both groups. The highest individual level of analgesia was T3 in the prone knee–chest group and T1 in the supine side horizontal group.

Recovery from spinal anaesthesia was similar in both groups, the median dermatomal level of pinprick analgesia was L2, 210 min after spinal block in both groups.

The mean maximum decrease in systolic arterial pressure from baseline was 30 mm Hg (SD 19, individual maximum decrease 66 mm Hg) in the prone knee–chest group compared with 13 mm Hg (SD 17, individual maximum decrease 79 mm Hg) in the supine side horizontal group. This difference, calculated using the Mann–Whitney *U* test, was significant ($P=0.0398$).

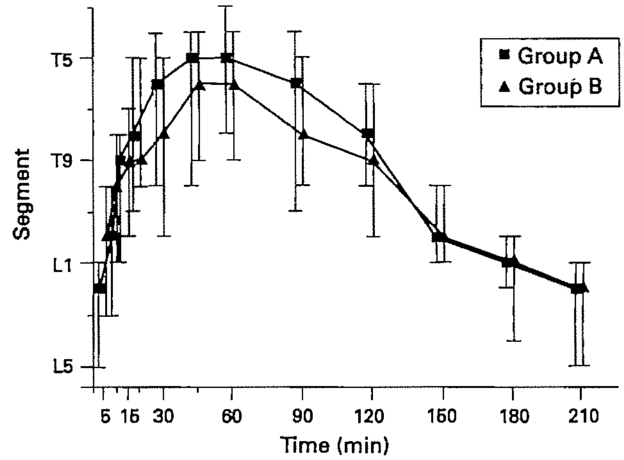

Figure 1 Spread of pinprick analgesia (median and quartiles) after subarachnoid injection of 3.0 ml of plain 0.5% bupivacaine at the L2–3 interspace. Group A=knee–chest position and group B=supine side horizontal position.

In the prone knee–chest group, ephedrine was needed in six patients compared with three in the supine side horizontal group. It should also be noted that vasopressors in the prone knee–chest group were not given earlier than 15 min from injection of the spinal anaesthetic. In the supine side horizontal group, all three patients needing vasopressor received it within the first 10 min from spinal injection.

Six patients in the prone knee–chest group needed atropine or glycopyrronium (four of these also received ephedrine) and two in the supine side horizontal group (one patient also received ephedrine) received atropine for bradycardia.

Because of mild incisional pain, the skin was infiltrated with local anaesthetic in one patient in the supine side horizontal group. One patient in the prone knee–chest group had insufficient cephalad spread of analgesia and was given an extra intrathecal dose of 1.0 ml of 0.5% bupivacaine 40 min after the initial spinal anaesthetic injection, before the start of operation. Another patient in the prone knee–chest group received 1.5 ml of 0.5% bupivacaine extradurally during surgery, 60 min after the intrathecal injection and was pain free within 2–3 min.

One patient in the prone knee–chest group had a sudden decrease in the level of analgesia from T12 to L3 after leakage of cerebrospinal fluid (CSF) through an unintentional tear in the dura. Soon after the patient complained of mild pain and was given two doses of fentanyl 50 μg.

Duration of surgery varied between 20 and 112 min (mean 56 min). The main complaint of patients

Table 1 Patient characteristics (mean (SD or range) or number)

	Sex (F/M)	Age (yr)	Height (m)	Weight (kg)	Duration of operation (min)
Prone knee–chest group	7/13	41 (24–57)	1.74 (0.08)	78 (17)	62 (25)
Supine side horizontal group	6/14	40 (24–61)	1.77 (0.09)	78 (4)	51 (19)

during surgery was numbness and ache in the arms and shoulders because of the position on the operating table. Seven patients (four in the prone knee–chest group, three in the supine side horizontal group) received light sedation, either diazepam 2.5–5.0 mg or midazolam 1.0–4.0 mg i.v. Two patients (both in the prone knee–chest group) also received a short infusion of propofol at a rate of 2 mg kg^{-1} h^{-1} or less near the end of operation.

All patients had complete sensory and motor recovery from spinal anaesthesia and none reported symptoms of radiating aching or pain in the buttocks or legs, or post-dural puncture headache (PDPH). None of the study patients reported backache or PDPH at a later stage. All patients were satisfied with this type of anaesthesia.

Discussion

We have found that there was no difference in the rate and spread of anaesthesia whether the subarachnoid local anaesthetic injection was performed with the patient in the horizontal side position or in the knee–chest position. However, when the patient was in the knee–chest position during induction of anaesthesia there was a tendency to greater hypotension and bradycardia compared with the horizontal position. It can be postulated that when the horizontal position is used for the first 20 min, patients have more time to accommodate to vasodilatation of the lower limbs. As was demonstrated in our earlier ultrasonographic study with healthy unanaesthetized volunteers,[3] there seems to be a tendency to venous blood pooling in the lower limbs in the knee–chest position. When this is combined with vasodilatation caused by anaesthesia the effect on venous return to the heart can be severely impaired.[5,6] In fact, even without anaesthesia, Wadsworth, Anderton and Vohra[4] were able to demonstrate a 20% reduction in cardiac index of volunteers placed in the knee–chest position.

The quality of anaesthesia was good for surgical purposes in all but one patient who needed an additional intrathecal dose of bupivacaine. Another patient received bupivacaine 7.5 mg into the exposed extradural space at the site of surgery 60 min after the original spinal anaesthesia. It is interesting that such a small extradural dose sufficed to abolish painful sensations within a few minutes, suggesting that this was a direct local effect on a painful spot rather than a spinal effect. The sedation needed in seven patients was based mostly on inconvenience felt in the hands and shoulders. Mild sedation with benzodiazepines or propofol appears to be beneficial in such cases. However, it is important that the depth of sedation is kept so light that the patient remains co-operative and maintains good spontaneous breathing.

The case of dural leakage during surgery was interesting. It was assumed that the dural lesion allowed leakage of CSF and local anaesthetic and this resulted in an immediate reduction in cephalic extension of sensory analgesia. After closure of the lesion the local anaesthetic seemed to have been redistributed within the cerebrospinal fluid and the previous level of analgesia was re-instated. The loss of some bupivacaine by leakage may have reduced the duration of block.

Spinal anaesthesia performed before the patient has assumed the surgical position has been a routine for low back operations, including laminectomy, lumbar disc operations and spinal fusions.[2,7,8] In a survey of 28 395 patients undergoing lumbar laminectomy for discogenic radiculopathy, Ramirez and Thisted reported that 7% of operations (1988 operations) were performed under spinal anaesthesia. No complications could be related exclusively to this technique.[9] In another retrospective review, Tezlaff and colleagues[2] reported 23 patients whose operations were performed during spinal anaesthesia, including laminectomies, lumbar disc operations and fusions. There were no failures of spinal anaesthesia, anaesthetic complications or PDPH.

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Pharmacokinetics of vecuronium during acute isovolaemic haemodilution

F. S. XUE, X. LIAO, S. Y. TONG, J. H. LIU, L. LI, Q. ZOU AND L. K. LUO

Summary

To evaluate the effect of acute isovolaemic haemodilution on the pharmacokinetics of vecuronium, we studied 13 patients undergoing haemodilution during surgery and 13 control patients. General anaesthesia was induced with thiopentone 4–6 mg kg^{-1} and fentanyl 2–4 μg kg^{-1}, and maintained with enflurane and 60% nitrous oxide in oxygen. The haemodilution patients underwent major elective plastic surgery with an anticipated surgical loss of more than 600 ml. Haemodilution was achieved by drainage of venous blood and i.v. infusion of lactated Ringer's solution and 6% dextran, during which the packed cell volume and haemoglobin concentration decreased from 45% to 28.1% and from 14.7 g dl^{-1} to 9.1 g dl^{-1}, respectively. After administration of a bolus of vecuronium 100 μg kg^{-1}, an improved fluorimetric assay was used to measure the plasma concentrations of vecuronium for 5 h. The results showed that the disposition kinetics of vecuronium were best described mathematically by a three-compartment open model in the two groups. The mean volume of the central compartment and volume of distribution at steady state were 42.3 (SD 11.8) ml kg^{-1} and 168.4 (31.5) ml kg^{-1}, respectively, in control patients, and significantly greater (55.2 (13.4) ml kg^{-1} and 225.9 (53.3) ml kg^{-1}) in the haemodilution patients ($P<0.05$). The elimination half-life was 50.3 (11.5) min in control patients and significantly greater (68.2 (15.1) min) in the haemodilution patients ($P<0.05$). The half-lives of fast distribution and distribution, mean residual time, area under the plasma concentration curve and plasma clearance were unchanged in patients who underwent haemodilution compared with the control group. (*Br. J. Anaesth.* 1997; **79**: 612–616).

Key words
Neuromuscular block, vecuronium. Pharmacokinetics, vecuronium. Blood, haemodilution.

Vecuronium is a non-depolarizing neuromuscular blocking agent with an intermediate clinical duration of action. In recent years, the possible factors influencing the pharmacokinetics of vecuronium, such as age,[1 2] hepatic[3] and renal[4 5] insufficiency, pregnancy[6] and hypothermia,[7] have been studied extensively. Preoperative isovolaemic haemodilution, which is an effective method of reducing homologous blood transfusion during surgery, is often associated with haemodynamic changes, changes in regional organ blood flow, blood chemistry, blood volume and body fluid distribution.[8–13] Previous studies have shown that the potencies of suxamethonium, pancuronium and tubocurarine are increased and the duration of action prolonged, after preoperative normovolaemic haemodilution.[14 15] However, there are no studies on the pharmacokinetics of vecuronium during acute isovolaemic haemodilution in adult patients. In this study, we have measured plasma concentrations of vecuronium using an improved fluorimetric technique and observed the effect of acute isovolaemic haemodilution on the pharmacokinetics of vecuronium.

Patients and methods

After obtaining informed consent and approval from the hospital's Ethics Committee, we studied 13 patients undergoing acute isovolaemic haemodilution during surgery and 13 patients not receiving haemodilution. All patients were ASA I, aged 18–39 yr and were undergoing elective plastic surgery. The haemodilution patients underwent major plastic surgery with an anticipated surgical loss of more than 600 ml. Three patients underwent breast reconstruction with a free flap, five patients received extensive head and face plastic surgery, four patients had an abdominoplasty and one patient a maxillectomy. Patients with cardiac and respiratory diseases were excluded. None suffered any disease or were receiving any drug known to alter neuromuscular function. Those with anaemia (haemoglobin concentration <12 g dl^{-1}) were also excluded.

Patients were premedicated with diazepam 0.2 mg

F. S. XUE, MD, FCAA, X. LIAO, MD, FCAA, S. Y. TONG, MD, FCAA, J. H. LIU, MD, FCAA, L. LI, MB, Q. ZOU, MD, FCAA, L. K. LUO, MD, FCAA, Department of Anaesthesiology, Plastic Surgery Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Ba-Da-Chu Road, Shi-Jing-Shan District, Beijing, People's Republic of China, 100041. Accepted for publication: June 10, 1997.

Correspondence to F. S. X.

kg^{-1} and atropine 0.01 mg kg^{-1} i.m., 1 h before anaesthesia. On arrival in the operating room, an i.v. catheter was inserted and general anaesthesia was induced with thiopentone 4–6 mg kg^{-1} and fentanyl 2–4 μg kg^{-1}. After topical anaesthesia with 2% lignocaine, the trachea was intubated without the aid of a neuromuscular blocking agent, and general anaesthesia was maintained with enflurane (1.5–2% expired concentration) and 60% nitrous oxide in oxygen. Fentanyl 2 μg kg^{-1} i.v. was supplemented as required. The lungs were ventilated (V_T=8–10 ml kg^{-1}, f=8–10 bpm) during surgery and $P_{E'CO_2}$ was maintained within normal limits.

After stable anaesthesia had been achieved in the haemodilution patients, 12–15 ml kg^{-1} of blood (approximately 20% of blood volume) were obtained from a cubital vein over a period of 15–20 min before the start of surgery and stored in a reservoir bag containing ACD solution. Simultaneously, a volume of Ringer's lactate solution, double or triple that of the withdrawn blood, and an equal volume of 6% medium molecular dextran (molecular weight 70 000 Da) were infused rapidly via a separate venous cannula. The packed cell volume (PCV) target after haemodilution was 25–30%. During surgery, blood loss was measured by swab and drape weighing and from suction bottles, and was replaced with Ringer's lactate solution and medium molecular dextran. Blood was reinfused only after major surgical loss was complete in the reverse order of collection through non-filtered infusion sets. Control patients only received Ringer's lactate solution 10–12 ml kg^{-1} h^{-1} during surgery. Haemodynamic variables remained stable throughout the study in all patients.

During surgery ECG, arterial pressure, heart rate, temperature and Sp_{O_2} were monitored continuously (Cardiocap, Datex Instrumentarium, Helsinki, Finland). Inspired and end-tidal concentrations of oxygen, carbon dioxide and nitrous oxide were measured and displayed digitally by an anaesthetic gas monitor (anaesthesia gas monitor type 1304, Bruel and Kjaer, Denmark). A cannula was placed in the radial or femoral artery for sampling. Arterial pH, Pa_{O_2}, Pa_{CO_2}, PCV and haemoglobin concentration were measured with a blood-gas electrolyte analyser (Model-5, Nova Biomedical Company, Hoboken, USA) before and during anaesthesia. Total plasma protein (TPP) and albumin (Alb) concentration were also measured using an automatic biochemical analyser (Type-550, Corning Medical Company, Oberlin, Ohio, USA). Body core temperature was maintained at 36–37 °C.

PLASMA SAMPLING

When anaesthesia was stable or haemodilution was complete, an i.v. bolus of vecuronium 100 μg kg^{-1} was administered. Blood samples (4 ml) were collected from an antecubital vein before and at 1, 3, 5, 10, 15, 20, 30, 45, 60, 90, 120, 180, 240 and 300 min after administration of vecuronium. Each blood sample was centrifuged within 5 min, and 1 ml of plasma was acidified immediately by adding 150 μl of NaH_2PO_4 1 mol $litre^{-1}$ to prevent hydrolysis of vecuronium. Spontaneous hydrolysis of vecuronium in plasma occurs at body pH and room temperature at a rate of 0.35% when determined in our laboratory. The samples were then frozen at −20 °C until subsequent analysis. Plasma concentrations of vecuronium were measured by a modified fluorimetric assay described originally for pancuronium by Kersten, Meijer and Agoston.[16] The fluorescent intensity of the sample was measured by a spectrofluorophotometer (model RF450; Shimadzu Corporation, Japan). The lower limit of sensitivity of this technique was 5 ng ml^{-1} for vecuronium. The coefficients of variation at concentrations of 10 (n=8), 250 (n=10) and 1000 ng ml^{-1} (n=10) were 9.7%, 4% and 0.5%, respectively, in our laboratory. None of the drugs used during anaesthesia interfered with assay of vecuronium.

PHARMACOKINETICS ANALYSIS

Individual data points from the time–plasma concentration curve of vecuronium were stored on a computer and analysed with a $3P_{87}$ program edited by the Chinese Association of Mathematical Pharmacology (Beijing, People's Republic of China). Plasma vecuronium concentration–time data were fitted to both two- and three-compartment mammillary pharmacokinetic models using non-linear, least-squares regression. Models were compared statistically using the F test to determine the simplest model which accounted for the data of each patient. In all patients, a three-compartment pharmacokinetic model was preferred statistically to a two-compartment model, using the technique of Boxenbaum, Riegelmann and Elashoff.[17] Therefore, the following variables were calculated using standard formulae from the $3P_{87}$ program: half-lives of rapid distribution ($T_{1/2}{}^{\pi}$), distribution ($T_{1/2}{}^{\alpha}$) and elimination ($T_{1/2}{}^{\beta}$), volume of the central compartment (V_c), volume of distribution at steady state (V^{ss}), area under the plasma concentration curve (AUC), mean residual time (MRT) and plasma clearance (Cl).

A POMS statistical software version 2.00 (Shanghai Scientific and Technical Publishers, Shanghai, People's Republic of China) was used for statistical analysis of the data. A chi-square test was used to compare sex distribution between the two groups. Other statistical analyses were made with the two-tailed non-parametric Mann–Whitney U test. $P<0.05$ was considered significant.

Results

There was no statistically significant difference between the two groups in age, body weight, height, preoperative temperature or duration of operation. Compared with preoperative values, concentrations of haemoglobin, PCV, total plasma protein and albumin during surgery decreased significantly in patients who had haemodilution but remained stable in the control group (table 1). Changes in arterial pH, Pa_{O_2} and Pa_{CO_2} in all the patients remained within normal limits throughout the study.

Compared with controls, plasma concentrations

Table 1 Patient characteristics of those who underwent ($n=13$) or did not have ($n=13$) haemodilution before and during surgery. Hb=Haemoglobin; PCV=packed cell volume; TPP=total plasma protein; Alb=albumin. Data are mean (SD). $^*P<0.05$, compared with preoperative data; $^\dagger P<0.05$, compared with controls

	Control		Haemodilution	
	Before op.	During op.	Before op.	During op.
Sex (M/F)	6/7		7/6	
Age (yr)	22		24	
Weight (kg)	58.7 (10.2)		60.1 (11.4)	
Height (cm)	168.5 (6.1)		170.1 (5.9)	
Rectal temperature (°C)	36.5 (0.05)		36.6 (0.07)	
Duration of surgery (h)	5.2 (1.4)		4.9 (1.7)	
Hb (g dl^{-1})	14.8 (1.2)	14.5 (1.0)	14.7 (1.0)	9.1 (1.2)*†
PCV (%)	45.2 (5.2)	43.8 (6.3)	45.0 (3.8)	28.1(5.9)*†
TPP (g $litre^{-1}$)	70.1 (6.8)	69.4 (5.5)	69.5 (4.9)	48.5 (8.9)*†
Alb (g $litre^{-1}$)	40.1 (3.2)	39.3 (5.5)	41.2 (5.1)	29.2 (4.7)*†

Table 2 Vecuronium pharmacokinetics in controls and haemodilution patients during surgery. $T_{1/2}^{\pi}$=Half-life of fast distribution; $T_{1/2}^{\alpha}$=distribution half-life; $T_{1/2}^{\beta}$=elimination half-life; V_c=volume of the central compartment; V^{ss}=volume of distribution at steady state; AUC=area under the plasma concentration curve; MRT=mean residual time; *Cl*=plasma clearance (mean (SD)). $^*P<0.05$ compared with controls

	Controls ($n=13$)	Haemodilution ($n=13$)
$T_{1/2}^{\pi}$ (min)	1.5 (0.58)	1.6 (0.9)
$T_{1/2}^{\alpha}$ (min)	12.1 (4.8)	14.1 (3.8)
$T_{1/2}^{\beta}$(min)	50.3 (11.5)	68.2 (15.1)*
V_c (ml kg^{-1})	42.3 (11.8)	55.2 (13.4)*
V^{ss} (ml kg^{-1})	168.4 (31.5)	225.9 (53.3)*
AUC (μg ml min)	33.3 (8.4)	30.4 (8.9)
MRT (min)	56.8 (13.4)	63.4 (18.2)
Cl (ml kg^{-1} min^{-1})	3.1 (1.0)	3.7 (1.5)

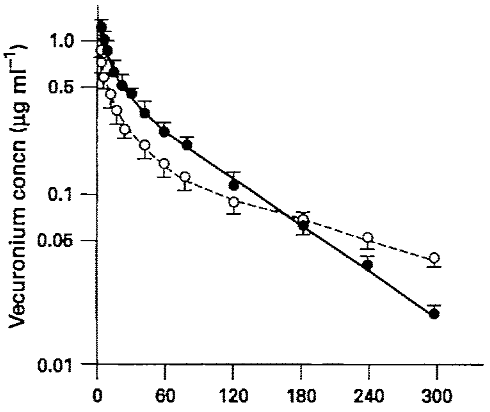

Figure 1 Plasma concentration–time curves for vecuronium in controls (●) and in patients who underwent acute isovolaemic haemodilution (○) after a single i.v. injection of vecuronium 100 μg kg^{-1} (mean, SEM).

of vecuronium in the haemodilution patients were lower during the initial 120 min after administration of the drug, but were higher from 120 to 300 min (fig. 1). Mean plasma concentrations of vecuronium were significantly different between the two groups at each time, except at 120, 180 and 240 min.

The concentration–time data for all patients were well described by a three-compartment open model. The pharmacokinetics of vecuronium for the two groups are summarized in table 2. In the haemodilution patients, V_c and V^{ss} were greater ($P<0.05$) and the elimination half-live ($T_{1/2}^{\beta}$) was longer ($P<0.05$) compared with controls. The half-lives of rapid distribution ($T_{1/2}^{\pi}$) and distribution ($T_{1/2}^{\alpha}$), AUC, MRT and *Cl* were not significantly different between the two groups.

Discussion

In this study, a classical fluorimetric assay was used to determine the plasma concentration of vecuronium: the lower limit of sensitivity of the method is 5 ng ml^{-1}, which is sufficient to detect vecuronium in plasma for up to 5 h after a bolus of 100 μg kg^{-1}. This fluorimetric assay had been used extensively to study the pharmacokinetics of vecuronium in children and adults,[1 4 18 19] but as it measures both vecuronium and its deacetylated metabolites, its lack of specificity could be criticized. In previous studies[1 4] thin layer chromatography was conducted after the assay to separate and estimate the proportion of metabolites. Even in adults with chronic renal failure,[4] none of the metabolites could be detected in plasma at any time. However, comparison between the fluorimetric and the more specific high-pressure liquid chromatography method (HPLC)[20] suggests that metabolites may account for 15% of the total plasma concentration of vecuronium over a range of 200–1000 ng ml^{-1}. But even if the presence of low concentrations of vecuronium metabolites slightly altered the pharmacokinetic data, there is no reason to suggest that such metabolites may be present in a greater proportion in haemodilution patients than in controls. Thus we believe that comparison of the pharmacokinetic data between the two groups is valid. Previous studies have suggested that the pharmacokinetics of vecuronium measured by fluorimetric assay were similar to those determined by HPLC or gas chromatography.[1 16] Furthermore, the pharmacokinetic data of vecuronium obtained in controls were within the range of those reported in previous studies.[5 6 18 19 21]

The most important difference between the control patients and those undergoing haemodilution was the greater volume of distribution of vecuronium in patients receiving haemodilution. Our data showed that in comparison with controls, the volume of the central compartment and volume of distribution of vecuronium at steady state in patients undergoing haemodilution increased by 33.4% and 25.5%, respectively. After administration of vecuronium 100 μg kg^{-1}, mean plasma concentrations of vecuronium in controls were 1.78 μg ml^{-1} at 1 min and 1.05 μg ml^{-1} at 3 min respectively, which were significantly higher than those in the haemodilution patients (1.14 μg ml^{-1} and 0.89 μg ml^{-1}; $P<0.05$). Vecuronium is a water soluble non-depolarizing neuromuscular blocking agent. It distributes mainly in extracellular fluid after i.v. administration.[22] Possible explanations for our results include rapid infusion of large volumes of crystalloid and colloidal solutions markedly increasing blood volume.[8] Haemodilution also decreases blood viscosity, increases cardiac output and velocity of blood flow. Thus blood flow to vessel organs such as the liver, lungs, kidneys, heart and brain is increased, possibly increasing metabolism and excretion of drugs.[9–11] In addition, haemodilution decreases plasma colloid oncotic pressure because of a decrease in plasma protein concentration. A large quantity of infused crystalloid solution could therefore enlarge the extracellular fluid volume.[12]

Vecuronium is eliminated mainly by the liver, and to a lesser extent unchanged by the kidney.[4 18] In this study, plasma clearance of vecuronium in patients undergoing haemodilution increased by 16.2%. This may be a result of the increase in hepatic and renal blood flow during haemodilution.[10 13] In addition, decreased plasma protein concentration during haemodilution might increase the ratio of unbound to bound vecuronium in plasma. As only free drug is filtered at the glomerulus, renal elimination may be increased. However, the difference in plasma clearance between the two groups was not statistically significant, which might be related to the small sample size and large individual differences. Although the elimination half-life of a drug is inversely proportional to plasma clearance (which was increased in the haemodilution patients), the elimination half-life of vecuronium was markedly prolonged in the haemodilution patients. This may be related to their larger volume of distribution at steady state.

In this study, the decay in plasma concentrations of vecuronium occurred in a triexponential manner, in contrast with that described in earlier studies[5 21 23] where plasma concentrations declined biexponentially. Possible factors that may explain this discrepancy are differences in the methods used to measure drug concentrations, different doses of vecuronium or duration of plasma sampling. In one study,[23] plasma concentrations of vecuronium measured by a relatively insensitive HPLC method (lower limit of detection 50 ng ml^{-1}) were observed for only 90 min after injection of vecuronium. Consequently, the larger part of the slower, terminal elimination phase was probably not detected. In another study, also using HPLC,[5] a larger dose of vecuronium (0.28 mg kg^{-1}, five times the recommended ED_{95} dose) was used in order to measure plasma concentrations for a longer period. A large dose of a drug can, in principle, lead to non-linear pharmacokinetic processes, with a consequent shallow rate of decay in the early phases of plasma concentration decline, and the merging of the early and late distribution slopes. Perhaps for this reason Fahey and colleagues[5] selected a biexponential function to describe the plasma decay curve of vecuronium, even though they detected the plasma decay curve of vecuronium for 4 h. In the study of Lebrault and colleagues[21] using a fluorimetric assay with a lower limit of sensitivity of 25 ng ml^{-1}, not only was a larger dose of vecuronium administered (0.2 mg kg^{-1}, 3.6 times the recommended ED_{95} dose), but plasma concentrations were observed for a shorter period (210 min) compared with our study.

However, in studies using very sensitive mass spectral analysis (level of detection 2 ng ml^{-1})[23] or a modified fluorimetric assay (level of detection 5 ng ml^{-1})[19] to measure plasma concentrations after administration of vecuronium 25–50 μg kg^{-1} or 100 μg kg^{-1} for 5–8 h, the authors found that the disposition kinetics of vecuronium were best described by a model with three compartments and with pharmacokinetic variables that agreed closely with those generated in this study. Mass spectrometry is the most sensitive assay method available to date and it specifically measures only unchanged vecuronium (or any of its metabolites, if so desired). Therefore, the results of this study support the views of Bencini and co-workers[4] that vecuronium disposition kinetics are best described by a three-compartment open model.

Early studies showed that the duration of neuromuscular effect after moderate doses of vecuronium (100 μg kg^{-1}) is governed by the distribution phase rather than the elimination phase. However, after a large dose (200–300 μg kg^{-1}) or repeated doses, recovery from paralysis probably occurs during the elimination phase.[22] On the basis of our results, it was assumed that compared with controls, the larger distribution volume of vecuronium in the haemodilution patients would result in lower plasma concentrations and thus increased dose requirements to achieve comparable neuromuscular block. In addition, the clinical duration of a lower dose of vecuronium may be shorter in patients undergoing haemodilution than in controls because of the larger distribution volume at steady state and higher plasma clearance. But after large or repeated doses, the clinical duration of vecuronium in the haemodilution patients may be prolonged because of the longer elimination half-life.

However, it must be remembered that haemodilution may also be associated with significant changes in plasma protein concentrations. The pharmacological effect of a drug is highly dependent on its degree of plasma protein binding, as only unbound drug diffuses through membranes and is thus available for binding to receptors and exerting its pharmacological action. Schuh reported[14] that the potency of pancuronium was increased during haemodilution, which may be related to a decrease in plasma protein binding. As the protein-bound fraction of vecuronium (30%) is similar to that of pancuronium (29%),[24] any increase in the plasma concentration of unbound vecuronium during haemodilution may outweigh the influences of a larger volume of distribution and a higher plasma clearance on its neuromuscular blocking effects.

Acknowledgement

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LABORATORY INVESTIGATIONS

Effects of volatile anaesthetics on spontaneous action potential firing of cerebellar Purkinje cells *in vitro* do not follow the Meyer–Overton rule

B. ANTKOWIAK, H. HENTSCHKE AND K. KIRSCHFELD

Summary

We have investigated in rat brain slices the effects of the volatile anaesthetics enflurane, isoflurane and halothane on spontaneous discharge patterns and mean firing rates of cerebellar Purkinje cells. In the absence of these anaesthetics, Purkinje cells fired bursts of action potentials separated by quiescent periods lasting less than 2 s. Mean discharge rates were 10.8 (SEM 0.4) Hz at 23±1 °C and 25.6 (1.2) Hz at 35±1 °C. The agents exhibited qualitatively different effects when applied at concentrations corresponding to 1–3 MAC. Enflurane markedly lengthened burst and inter-burst durations. Isoflurane acted in a similar manner, but effects were less pronounced. In contrast with isoflurane and enflurane, halothane shortened burst durations. At concentrations corresponding to 1–1.5 MAC, halothane, isoflurane and enflurane significantly depressed action potential firing by 15–30% ($P<0.05$). Enflurane 1.2 mmol litre^{-1} (2.0 MAC), isoflurane 0.9 mmol litre^{-1} (2.8 MAC) and halothane 0.9 mmol litre^{-1} (3.8 MAC) depressed spontaneous spike rates by 50%. The changes in discharge patterns and the concentration-dependent decrease in the firing rates were similar at 23±1 °C and 35±1 °C. In summary, we observed that neither the anaesthetic-induced alterations in spontaneous discharge patterns nor the EC_{50} values of the concentration-dependent depression of the mean firing rates were in accordance with the Meyer–Overton rule. However, at clinically relevant concentrations, depression of average spike rates did not differ significantly between the anaesthetics and thus followed the rule. Our results suggest that anaesthetic actions, which are in accordance with the rule, are frequently masked by several side effects. (*Br. J. Anaesth.* 1997; **79**: 617–624).

Key words
Anaesthetics volatile, halothane. Anaesthetics volatile, isoflurane. Anaesthetics volatile, enflurane. Brain, cerebellum. Brain, Purkinje neurones. Theories of anaesthetic action, Meyer–Overton.

The efficacy of volatile general anaesthetics in depressing painful stimuli-evoked movements in mammals is predicted well by the Meyer–Overton rule which correlates the potency of these compounds with fat solubility.[1 2] For a molecular mechanism, possibly involved in the anaesthetic state, it is regarded as a prerequisite that the effects follow this rule.[3]

Anaesthetic-induced inhibition of motor responses, such as the righting reflex, seems to be related mainly to the depressant effects observed in the spinal cord.[4 5] Volatile anaesthetics also reduce neuronal activity in many other parts of the central nervous system, including the hippocampus,[6–11] neocortex,[12] thalamus[13 14] and olfactory cortex.[15 16] In several studies, the decrease in neuronal activity observed during anaesthesia was attributed to various mechanisms, for example activation of potassium channels,[17 18] depression of spike after hyperpolarizations,[12] inhibition of sodium channels,[19] depression of synaptic excitation[20] and potentiation of synaptic inhibition.[21] However, the question remains as to which of these examples follows the Meyer–Overton rule.

In the nervous system, information is coded into spike patterns and spike rates. We assume that anaesthetic-induced alterations in firing patterns of central neurones should be also in accordance with the rule, given that the underlying molecular mechanisms are related to the state of general anaesthesia. At present, little information is available on how volatile anaesthetics affect spike patterns in different parts of the central nervous system.

We have investigated the effects of halothane, isoflurane and enflurane on spontaneous action potential firing of cerebellar Purkinje neurones *in vitro*. Purkinje cells exhibit spontaneous activity even in acutely isolated brain slices.[22–24] This enabled us to test the Meyer–Overton rule by comparing the effects of three anaesthetics on discharge patterns and mean firing rates.

Materials and methods

DETERMINATION OF MAC VALUES

Anaesthesia was induced in 13–16-day-old Sprague Dawley rats of both sexes in Plexiglas boxes with a

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BERND ANTKOWIAK, PHD, HARALD HENTSCHKE, KUNO KIRSCHFELD, PHD, Max-Planck-Institut für biologische Kybernetik, Spemannstr. 38, 72076 Tübingen, Germany.
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Correspondence to B. A.

gas flow of approximately 2 litre min^{-1}. The desired vapour concentrations of volatile anaesthetics were delivered by calibrated vaporizers (Draeger, Germany). EC_{50} values for general anaesthesia were determined as described previously.[25]

PREPARATION OF CEREBELLAR BRAIN SLICES

Slices were prepared according to procedures similar to those described by Edwards and colleagues.[26] In brief, 13–16-day-old rats were anaesthetized deeply with enflurane, isoflurane or halothane, decapitated and the brains removed rapidly. Brains were stored for 10–12 min in ice-cold artificial cerebrospinal fluid (ACSF) consisting of (mmol litre^{-1}): NaCl 125, KCl 2.5, NaH_2PO_4 1.25, $MgCl_2$ 1, $NaHCO_3$ 26, $CaCl_2$ 2 and glucose 25. The cerebellum was glued onto a Teflon block and 250–300-μm thick sagittal slices were cut with a vibratome (Campdgen, UK). Slices were stored in a bath of ACSF at room temperature bubbled with 95% oxygen and 5% carbon dioxide. They were then transferred to the recording chamber 1–6 h later and perfused continuously with ACSF at a flow rate of approximately 1 ml min^{-1}.

STAINING OF PURKINJE CELLS

Neurones in cerebellar slices were filled with Biocytin by means of the patch–clamp technique.[27] Standard immunocytochemical methods were used for further processing.[27 28]

EXTRACELLULAR RECORDINGS

Slices were viewed under low magnification with an inverted microscope. The typical layering of sagittal cerebellar slices was well visible. ACSF-filled glass electrodes with resistances of approximately 5 MΩ were positioned on the surface of the Purkinje cell layer (fig. 2). They were advanced into the slices until extracellular spikes exceeding 300 μV in amplitude were observed and a single unit could be discriminated clearly. Noise amplitude was 20–100 μV.

CONTROL OF EXPERIMENTAL TEMPERATURE

Experiments were carried out at either 22–24 °C or 34–36 °C. The recording chamber consisted of a metal frame with a glass bottom. A heating wire was glued onto the metal frame. In cases where experiments were carried out at body temperature, the frame was heated by passing an appropriate DC current through the heating wire.

PREPARATION AND APPLICATION OF TEST SOLUTIONS

Test solutions were prepared by dissolving the anaesthetics in the ACSF according to the method described by Wakamori, Ikemoto and Akaike.[29] For calculating MAC values, the concentrations proposed by Franks and Lieb were used.[30] Thus 1 MAC corresponded to aqueous concentrations of halothane 0.25 mmol litre^{-1}, isoflurane 0.32 mmol litre^{-1} and enflurane 0.62 mmol litre^{-1}. Anaesthetics were applied via bath perfusion using syringe pumps (ZAK, Germany) which were connected via Teflon tubing to the experimental chamber. Flow rate was approximately 1 ml min^{-1}. When switching from ACSF to drug-containing solutions, the medium in the experimental chamber was replaced within 2 min by at least 95%. Effects on spike patterns were stable at approximately 5 min later. This delay may be attributed to diffusion of the test solution into the tissue. The time required to observe recovery increased with the concentration tested. With 0.5–2 MAC, full recovery was reached after 12–15 min and with 4–6 MAC after 30–60 min. For a single application, stable recording for at least 1 h was necessary.

DATA ANALYSIS

Data were low-pass filtered between 3 and 10 kHz, acquired on a PC with the digidata 1200 AD/DA interface and pClamp 6 software (Axon Instruments, USA) at 10–20 kHz. Simultaneously, records were stored on a Sony data recorder for further analysis. Extracellularly recorded spikes were counted on- or off-line using software event detectors. Spike rates were measured as mean spikes occurring in a period of 180–300 s. Inter-spike interval and burst analysis were performed by the pClamp program package. For statistical analysis the paired Student's *t* test was used. Unless otherwise stated, results are given as mean (SEM).

Results

SENSITIVITY OF ANIMALS TO VOLATILE ANAESTHETICS

In this study, brain slices were derived from 13–16-day-old Sprague–Dawley rats. We first assessed if these young animals and adult rats were equally sensitive to volatile anaesthetics. The

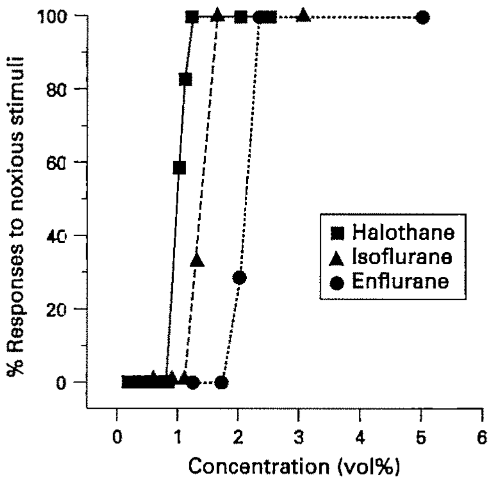

Figure 1 Effects of halothane, isoflurane and enflurane on painful stimuli-evoked movements of 2-week-old Sprague–Dawley rats which were used throughout the experiments. For each concentration, 15–20 animals were tested. EC_{50} values estimated from the dose–response curves are shown in table 1.

Table 1 Comparison of EC_{50}-values for general anaesthesia between about 2 week-old and adult Sprague Dawley rats. In the case of isoflurane the range given for adult rats indicates the variation in EC_{50}-values observed in the literature. References are given in brackets

	13–16-day old animals	Adult animals
Halothane	1.05 vol%	0.95 vol% [25]
Isoflurane	1.31 vol%	1.28–1.46 vol% [25, 31, 32]
Enflurane	2.10 vol%	1.95 vol% [25]

potencies of the anaesthetics were estimated from dose-dependent depression of painful stimuli-evoked movements according to a procedure reported previously.[25] The results summarized in figure 1 and table 1 show that, in the case of approximately 2-week-old rats, half-maximal depression by halothane, isoflurane and enflurane was observed at concentrations close to those reported for adult animals.[25 31–33]

EFFECTS OF VOLATILE ANAESTHETICS ON THE DISCHARGE RATES OF PURKINJE CELLS IN CEREBELLAR SLICES

Extracellular recordings were performed on 464 single Purkinje cells by positioning glass electrodes in sagittal cerebellar brain slices, as illustrated in figure 2A. Electrodes were advanced into the Purkinje cell layer until biphasic signals with amplitudes of approximately 0.2–1.0 mV could be discriminated clearly from baseline noise, which was usually less than 0.1 mV. In figure 2B a typical activity pattern, obtained at 23±1 °C, is shown. If inter-spike intervals lasting longer than 250 ms are considered as inter-burst intervals, the large unit fired bursts of action potentials separated by gaps of 0.2–2 s in duration. Bath application of tetrodotoxin 0.5 μmol $litre^{-1}$, which blocks Na^+ channels, reversibly suppressed these spontaneous voltage deflections (fig. 2B, $n=5$), indicating that they were generated by fast sodium spikes of a neurone close to the micropipette. To determine if the potency of the tested anaesthetics depended on a particular temperature, recordings were carried out at 23±1 °C or 35±1 °C. Increasing the temperature by approximately 10 °C shortened inter-burst durations and increased spontaneous firing rate by more than two-fold (fig. 2C, D).

In figure 3 representative examples of the effects of enflurane, isoflurane and halothane on firing pattern (fig. 3A) and discharge rate (fig. 3B) of a Purkinje cell

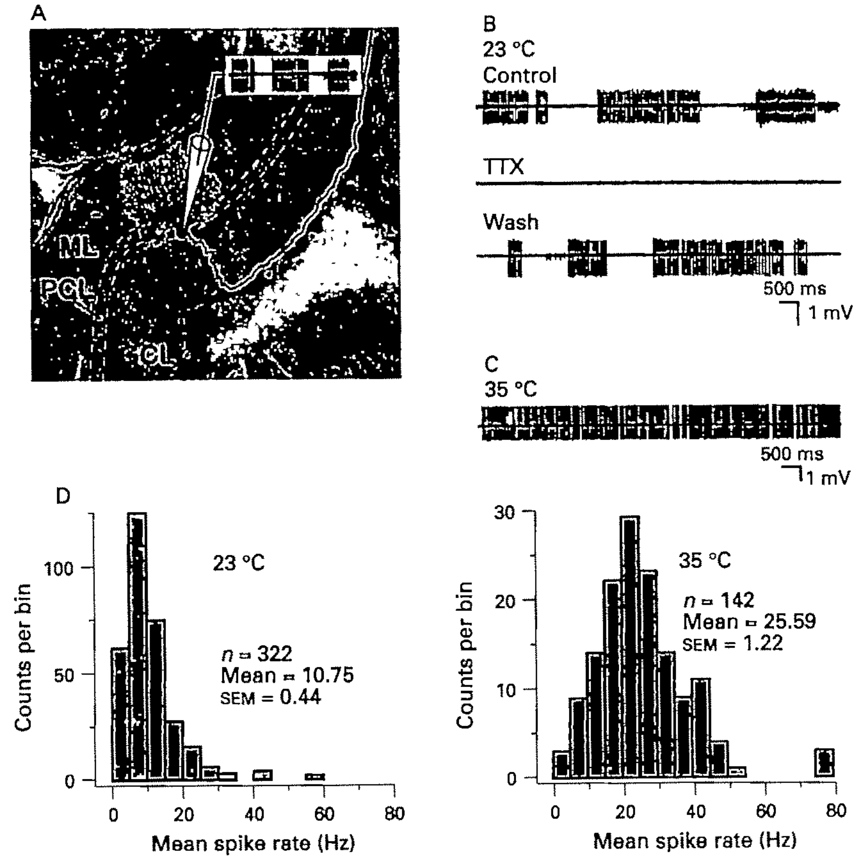

Figure 2 A· Photograph of a cerebellar brain slice, indicating the position of the Purkinje cells, layering and approach for obtaining extracellular recordings The Purkinje cell was labelled with Biocytin.[27 28] ML=Molecular layer; PCL=Purkinje cell layer; GCL=granule cell layer. Broken lines=approximate position of the Purkinje cell layer. Signals such as those indicated in the inset were obtained only when placing the recording electrode in the Purkinje cell layer where the somata of Purkinje cells lie densely packed. B: Extracellular recordings at 23±1 °C before, during and after treating the slice with tetrodotoxin (TTX). In the traces, two different cells can be discriminated easily by the different spike amplitudes. The neurones fired bursts of action potentials separated by gaps 0.2–5 s in duration. TTX 1 μmol $litre^{-1}$ reversibly depressed the occurrence of extracellularly recorded action potentials. C: Representative recording at 35±1 °C. Inter-burst durations shortened and mean spike rate increased. D: Distributions of mean spike rates obtained at 23±1 °C and 35±1 °C.

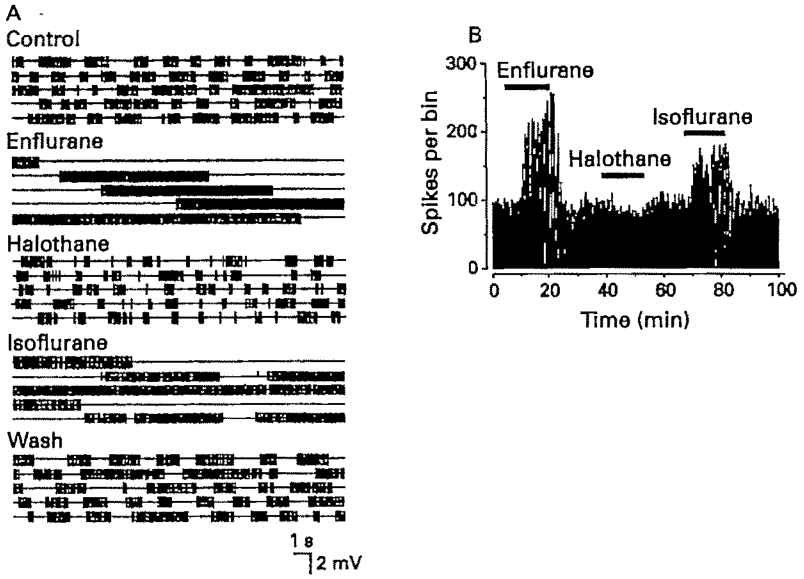

Figure 3 Effects of halothane 0.5 mmol litre^{-1}, isoflurane 0.64 mmol litre^{-1} and enflurane 1.24 mmol litre^{-1} on discharge patterns (A) and firing rates (B) of a cerebellar Purkinje cell. The concentrations corresponded to 2 MAC. The bin width in B was 10 s. The experiment was performed at 23±1 °C.

are shown. The anaesthetics were applied at concentrations twice as high as the EC_{50} value for general anaesthesia (2 MAC). They exhibited qualitatively different effects on the same neurone. Enflurane caused the cell to fire long bursts of action potentials, separated by gaps of approximately 10–20 s in duration. Spike patterns were similar in the presence of isoflurane, but burst and inter-burst durations were shorter (fig. 3B). In contrast with enflurane and isoflurane, halothane shortened burst durations and increased the firing rate within bursts. The effects were reversed on removing the anaesthetic.

The actions of volatile anaesthetics on the activity patterns of Purkinje cells were characterized further by comparing inter-spike interval histograms obtained from recordings carried out before, during and after treatment. The histograms shown in figure 4 were derived from three different cells. Under control conditions, all histograms exhibited a prominent peak at 50–100 ms and a smaller one at 1–2 s. These peaks corresponded to inter-spike intervals within the bursts and inter-burst durations

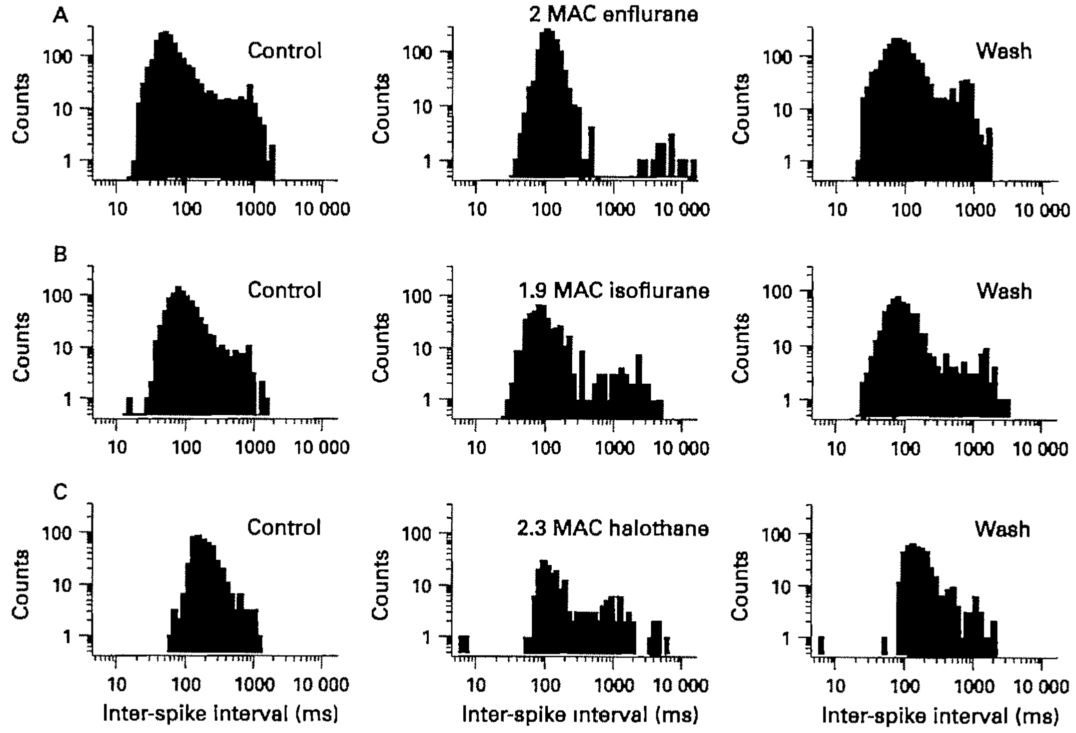

Figure 4 Inter-spike interval histograms derived from Purkinje cells in the absence and presence of volatile anaesthetics. The distributions were obtained from recordings which lasted 3 min. In these experiments the slices were exposed to enflurane 1.24 mmol litre^{-1} (A), isoflurane 0.61 mmol litre^{-1} (B) and halothane 0.57 mmol litre^{-1} (C). The corresponding MAC values are indicated.

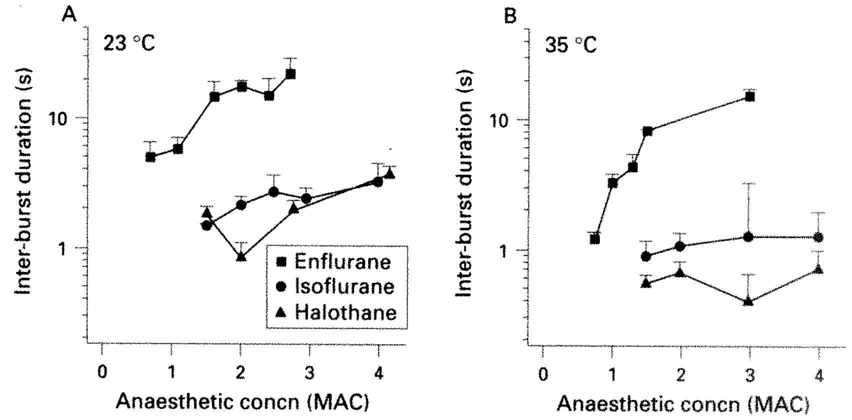

Figure 5 Effects of volatile anaesthetics on averaged inter-burst durations recorded at 23±1 °C and 35±1 °C. At both temperatures enflurane was most effective in increasing inter-burst durations. In the presence of 4 MAC of enflurane, spontaneous firing was suppressed completely (see fig. 6A).

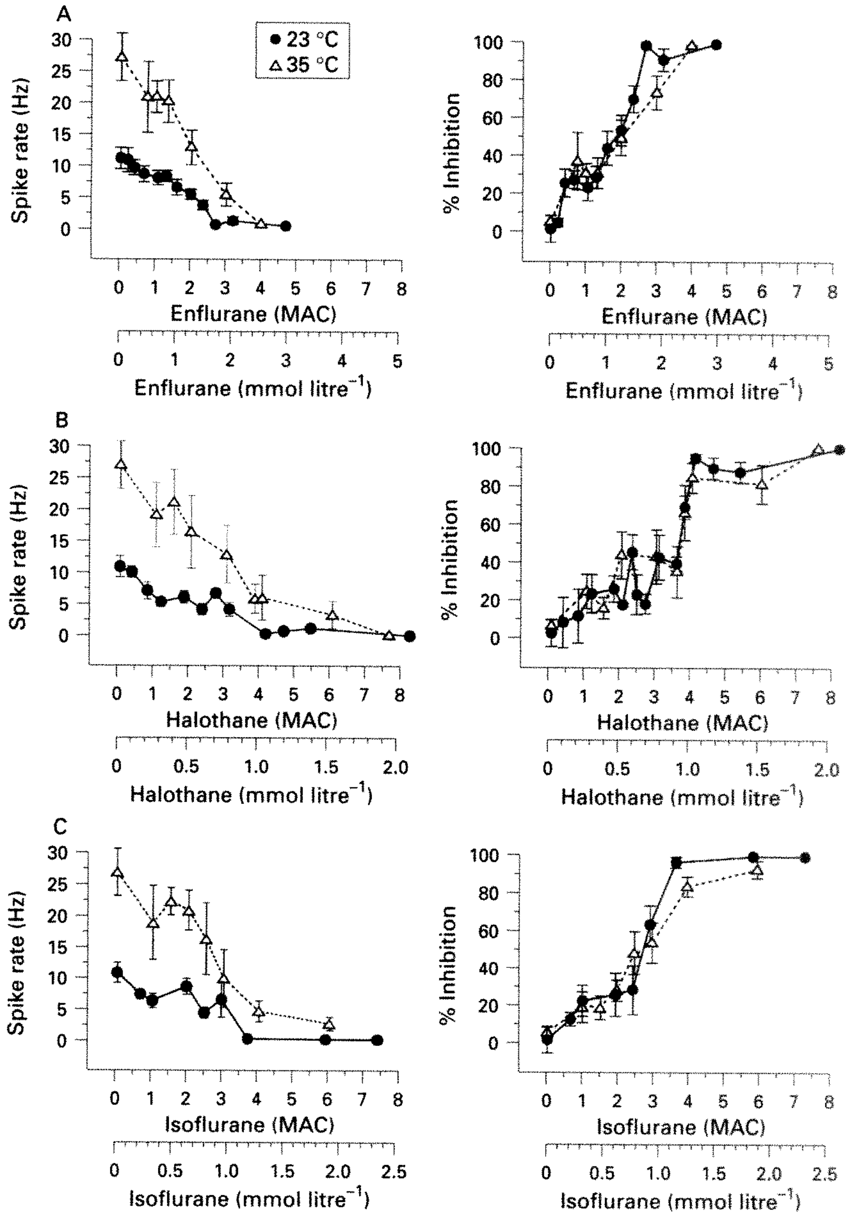

Figure 6 Concentration–response relationships for anaesthetic-induced depression of mean spike rates by enflurane (A), halothane (B) and isoflurane (C). Averaged spike rates monitored at 23±1 °C (●) and 35±1 °C (△) are shown in the left column. In the right column the effects of volatile anaesthetics were calculated by comparing action potential discharge rates before and during treatment.

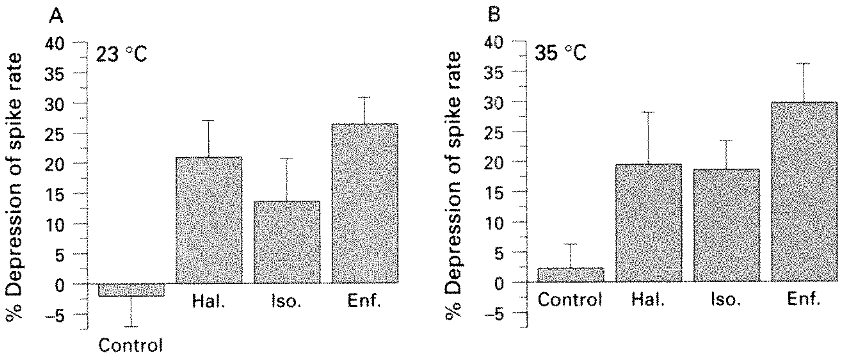

Figure 7 Depression of mean firing rates by clinically relevant concentrations of halothane (Hal.) isoflurane (Iso.) and enflurane (Enf.) at 23±1 °C and 35±1 °C. Data were pooled from those recordings in which concentrations corresponding to 1.0–1.5 MAC were applied. At both temperatures, the anaesthetics significantly depressed spontaneous spike rates ($P<0.05$).

Table 2 Half-maximal depression of spontaneous spike rates at 23±1 and 35±1°C. The corresponding MAC-values are given in brackets. Note that half-maximal depression occurred at similar anaesthetic concentrations, whereas the corresponding MAC-values differed considerably

	23±1 °C	35±1 °C
Halothane	0.9 mmol litre^{-1} (3.8 MAC)	0.9 mmol litre^{-1} (3.8 MAC)
Isoflurane	0.9 mmol litre^{-1} (2.8 MAC)	0.9 mmol litre^{-1} (2.8 MAC)
Enflurane	1.1 mmol litre^{-1} (1.8 MAC)	1.2 mmol litre^{-1} (2.0 MAC)

(for comparison see figs 2B and 3A). Inter-burst durations exceeding 3 s were not observed. The anaesthetics introduced long-lasting inter-burst intervals into the histograms; up to 12 s with enflurane and up to 7 s with isoflurane and halothane.

In figure 5, the concentration-dependent actions of volatile anaesthetics on the averaged inter-burst intervals are shown at different temperatures. The time criterion distinguishing between bursts and inter-bursts was set at 250 ms. The analysis was restricted to neurones exhibiting firing rates close to 10 Hz at 23±1 °C and to 25 Hz at 35±1 °C before exposing the cells to the anaesthetics. At both temperatures, enflurane increased inter-burst durations to approximately 10–20 s in a concentration-dependent manner. In the presence of halothane and isoflurane, inter-burst durations were 0.5–2 s. From the data shown in figures 3–5, it is evident that the effects of the anaesthetics were qualitatively different at both temperatures.

In spite of the discovery that anaesthetic-induced changes in the firing patterns of Purkinje cells did not follow the Meyer–Overton rule, it seemed possible that concentration-dependent depression of mean spike rates was in accordance with the predictions of the rule. In figure 6, the discharge rates and depression of spontaneous spiking are plotted against MAC values and concentrations of applied anaesthetics. Recordings were carried out at 23±1 °C and 35±1 °C. The effects at 0 MAC were obtained by applying ACSF and analysing the data according to the usual procedure. EC_{50} values interpolated from the concentration–response curves on depression of mean firing rates are summarized in table 2. The results displayed in figure 6 and table 2 show that although mean firing rates were affected considerably by changes in temperature, the relative decrease in spike rates caused by volatile anaesthetics were similar at both temperatures. Furthermore, EC_{50} values were not in accordance with the predictions of the Meyer–Overton rule (table 2).

The data presented in figure 6 demonstrate that, at least in the case of halothane and isoflurane, half-maximal inhibition of spike rates occurred at high concentrations, corresponding to approximately 3–4 MAC values. Although the decrease in spontaneous activity recorded at concentrations corresponding to 1.0–1.5 MAC was relatively low (15–30%), it was statistically significant for all anaesthetics (fig. 7). The data summarized in figure 7 show further that, at a range of clinically relevant concentrations depression of spike rates induced by enflurane, isoflurane and halothane did not differ significantly ($P<0.05$) and thus were in accordance with the predictions of the Meyer–Overton rule.

Discussion

COMPARSION WITH RELATED STUDIES

Nicoll and Madison analysed the effects of general anaesthetics on hippocampal and spinal neurones.[34] They observed that when cells were exposed to anaesthetics, membrane resting potential hyperpolarized and input resistance decreased. The results suggested that the efficacies of the agents were in accordance with the Meyer–Overton rule. Unfortunately, in this study concentrations 10 times higher than those required to produce anaesthesia were used.

The effects of halothane, isoflurane and enflurane in the hippocampus slice preparation were evaluated by Fujiwara and co-workers.[8] The authors found that at clinically relevant concentrations the order of anaesthetic potencies was not consistent with MAC values. As demonstrated in this study, anaesthetic-induced changes in firing patterns differed with respect to the agent used.

As reviewed recently, the actions of volatile anaesthetics in the spinal cord rather than those on higher brain structures seem to be responsible for depression of painful stimuli-evoked motor responses.[5] As the latter is predicted well by the Meyer–Overton rule, one might expect inhibition of the neuronal circuits in the spinal cord, mediating these movements, to also be in accordance with the rule. However, even here, several aspects of anaesthetic actions did not follow the rule.

In this study, we have provided evidence that halothane, isoflurane and enflurane, if applied at equal MAC values, alter the firing patterns of cerebellar Purkinje cells in different manners. Furthermore, the EC_{50} values, estimated from concentration-dependent depression of mean discharge rates, were not in accordance with the predictions of the rule. These two results cannot be explained by an unspecific mechanism, as suggested by the lipid theory.[3 35 36] Our findings in cerebellar slices argue against a unitary mechanism of anaesthetic action in this system and indicate specific effects. From the results on hippocampal, spinal and cerebellar neurones, it must be concluded that in the mammalian central nervous system effects of volatile anaesthetics which follow the Meyer–Overton rule are an exception rather than a common observation.

EFFECTS OF TEMPERATURE

Comparison of investigations elucidating the actions of volatile anaesthetics on central neurones is difficult since, because of methodological considerations, some studies were carried out at room temperature while others were conducted at body temperature.[37] It remains unclear to what extent the reported effects depended on the particular temperature chosen in the experiments. Our data indicate that the effects monitored at room temperature provide a reliable approximation for the effects at body temperature. Although increasing the temperature by approximately 10 °C more than doubled the spontaneous spike rate (fig. 2D), neither depression of mean firing rates (fig. 6) nor anaesthetic-induced alterations in discharge patterns (fig. 5) differed considerably between temperatures. A similar conclusion with regard to temperature dependence was obtained from a study on the actions of enflurane on GABA-mediated inhibitory postsynaptic currents (IPSC) monitored from voltage-clamped Purkinje neurones.[38] Although increasing the temperature from 23 to 35 °C reduced current decays of IPSC by 50%, the action of 1 and 2 MAC enflurane on IPSC kinetics proved to be temperature independent.

MOLECULAR MECHANISMS OF ANAESTHETIC ACTION IN CEREBELLAR SLICES

It is commonly assumed that the molecular mechanisms underlying general anaesthesia occur in a range of clinically relevant concentrations and are in accordance with the Meyer–Overton rule. In spite of considerable research efforts, these mechanisms are still a matter of controversy.[3 18 19 21] There is growing evidence that the $GABA_A$ receptor ion channel complex is a good candidate for such a mechanism.[3 21] We demonstrated recently that enflurane decreased action potential firing of Purkinje cells in acutely isolated cerebellar slices by increasing $GABA_A$-mediated synaptic inhibition.[38] At anaesthetic concentrations corresponding to 0.5–1.5 MAC, enflurane enhanced synaptic inhibition by approximately two-fold and thereby reduced the discharge rate by 20–30% (fig. 7 in Antkowiak and Heck[38]). As shown elsewhere, the actions of volatile anaesthetics on the $GABA_A$ receptor seem to follow the rule. This is consistent with the finding that at 1.0–1.5 MAC the decrease in firing rate of Purkinje cells was approximately similar for halothane, isoflurane and enflurane (see fig. 7). However, apart from the actions on $GABA_A$ receptors, clinically relevant concentrations of enflurane affected further ionic conductances of Purkinje neurons (figs 12, 13 in Antkowiak and Heck[38]). At 0.5–2.0 MAC these effects considerably changed the discharge patterns of Purkinje cells, but did not alter mean discharge rates. Thus enflurane-induced firing patterns of Purkinje cells and the decrease in the firing rate were caused by different molecular actions of the anaesthetic operating in parallel. At least one of these effects (potentiation of GABA-mediated inhibition) seems to follow the rule, but others do not. This explains why anaesthetic-induced changes in discharge patterns shown in figure 3 are not in accordance with the rule.

Antkowiak and Heck further excluded the fact that increased $GABA_A$-mediated inhibition contributed considerably to depression of firing rates measured at 2–7 MAC.[38] At these high concentrations, the anaesthetic abolished action potential firing of presynaptic GABAergic interneurones and thereby reduced $GABA_A$-mediated synaptic inhibition (figs 6 and 7 in Antkowiak and Heck[38]). At concentrations of 2–7 MAC, further depressant actions come into play.[3] Assuming different mechanisms of anaesthetic action, which contribute to concentration-dependent reduction in average discharge rates, also explains the biphasic nature of the curves in figure 6. It seems possible that activation of potassium channels, as observed in hippocampal, spinal and thalamic neurones, is involved, but other mechanisms, such as block of sodium channels, cannot be excluded.[3]

In conclusion, our results may help to explain why so many studies on brain slices fail to identify mechanisms which follow the Meyer–Overton rule. The latter should not lead to the conclusion that anaesthetic actions, which are in accordance with the rule, do not occur in these preparations. We suggest that effects which are relevant for general anaesthesia and which mediate painful stimuli-evoked motor responses (fig. 1) are frequently masked by side effects. As observed previously, research will have to concentrate on the problem of distinguishing between relevant and side effects.[3] The vast majority of studies concerning the mechanisms that underlie general anaesthesia have been carried out *in vitro*. It is noteworthy, however, that the few *in vivo* investigations available on this topic have reported similar phenomena.[5]

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Comparison of the effects of isoflurane with those of propofol on pulmonary vascular impedance in experimental embolic pulmonary hypertension

P. EWALENKO, S. BRIMIOULLE, M. DELCROIX, P. LEJEUNE AND R. NAEIJE

Summary

Inhaled but not i.v. anaesthetics are reported to decrease pulmonary vascular resistance. The aim of this study was to compare the effects of isoflurane with those of propofol on the interaction between right ventricular (RV) function and the pulmonary vascular system in embolic pulmonary hypertension. Nine dogs received in random sequence propofol 18 mg kg^{-1} h^{-1} and 1.4% end-tidal isoflurane. Pulmonary haemodynamic state was evaluated by pulmonary arterial pressure/flow (PAP/$\dot{Q}$) plots and pulmonary vascular impedance (PVZ) spectra. Right ventricular function was assessed by total hydraulic power (*W*tot), ratio of oscillatory power (*W*osc) to *W*tot, and d*P*/d*t*max. Measurements were obtained, with both anaesthetics, before and after pulmonary embolic hypertension induced by autologous blood clots. Embolism increased PAP, 0 Hz and low frequency input impedance, displaced first minimum of PAP/$\dot{Q}$ moduli and zero crossing of phase to higher frequencies, decreased characteristic impedance, decreased *W*osc/*W*tot without affecting *W*tot, and increased d*P*/d*t*max. Compared with propofol, isoflurane at baseline did not affect PAP/$\dot{Q}$ plots, PVZ or hydraulic power data, but decreased d*P*/d*t*max. After embolism, isoflurane shifted PAP/$\dot{Q}$ plots to lower PAP without affecting PVZ, did not affect hydraulic power data and decreased d*P*/d*t*max. We conclude that in canine embolic pulmonary hypertension, isoflurane compared with propofol impeded RV vascular coupling caused by decreased RV contractility, while afterload remained unchanged despite some decrease in pulmonary vascular tone. (*Br. J. Anaesth.* 1997; **79**: 625–630).

Key words
Anaesthetics volatile, isoflurane. Anaesthetics i.v., propofol. Embolism, pulmonary embolism. Cardiorespiratory system, effects. Lung, function.

General anaesthesia is commonly associated with decreased systemic arterial pressure caused by a combination of negative inotropism and vasodilatation. While inhalation and i.v. agents have broadly comparable effects on systemic haemodynamic state, inhaled but not i.v. anaesthetics have been reported to inhibit hypoxic pulmonary vasoconstriction (HPV). This pulmonary vascular effect of inhalation agents is prominent in isolated perfused lung preparations *in vitro*,[1] but less so in more intact animal preparations.[2 3] We reported previously that anaesthesia with inhaled isoflurane compared with i.v. propofol decreased pulmonary vascular tone in hypoxia and hyperoxia, without inhibiting HPV, and that isoflurane-induced pulmonary vasodilatation did not affect pulmonary vascular impedance (PVZ) in intact dogs.[4] However, hypoxia-induced pulmonary hypertension was mild, with pulmonary artery pressure (PAP) seldom exceeding 20 mm Hg,[4] so that the pulmonary vasodilating properties of isoflurane would not be expected to be important. We therefore investigated the pulmonary haemodynamic effects of isoflurane anaesthesia in more severe experimental pulmonary hypertension, such as that induced by autologous blood clot embolization in dogs.

In this study, we characterized the flow-resistive properties of the pulmonary circulation by multipoint mean PAP compared with mean pulmonary blood flow ($\dot{Q}$) relationships, and evaluated right ventricular (RV) afterload by measurement of PVZ. Associated changes in RV function were assessed by the maximum rate of pressure increase (d*P*/d*t*max) and total (*W*tot) and oscillatory (*W*osc) hydraulic power. The measurements were performed before and after induction of autologous blood clot embolism in dogs anaesthetized with either isoflurane or propofol. Propofol was chosen because it does not act as a pulmonary vasodilator[4 5] and because of its very short duration of action, allowing comparisons with isoflurane in the same animal. The hypothesis tested was that isoflurane, despite its negative inotropic properties, would decrease pulmonary vascular resistance (PVR) sufficiently to

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P. EWALENKO, MD, PHD, Department of Anaesthesia and Intensive Care, Jules Bordet Institute, Free University of Brussels, 1 rue Heger Bordet, B-1000 Brussels, Belgium. S BRIMIOULLE, MD, PHD, R. NAEIJE, MD, PHD, Department of Intensive Care, Erasme University Hospital, 808 route de Lennik, B-1070 Brussels, Belgium. M. DELCROIX, MD, PHD, Department of Pneumology, UZ Gasthuisberg, 49 Herestraat, B-3000 Leuven, Belgium. P. LEJEUNE, MD, PHD, Department of Intensive Care, Vesale Institute, 706 route de Gozée, B-6110 Montigny -le-Tilleul, Belgium. Accepted for publication. July 1, 1997.

Correspondence to P. E.

decrease ventricular afterload, thereby not altering ventriculo-vascular coupling.

Materials and methods

All experiments were conducted in accordance with the "Guiding Principles in the Care and Use of Animals" approved by the American Physiological Society. We studied 12 mongrel dogs (weight 20–36 kg, mean 27 kg) anaesthetized with propofol 10 mg kg^{-1} i.v. followed, in random order, by either 1.4% end-tidal inhaled isoflurane (=1 MAC for the dog) or propofol 18 mg kg^{-1} h^{-1} i.v. The lungs of the dogs were ventilated with an inspired oxygen fraction ($F_{I_{O_2}}$) of 0.4, 12 bpm and a tidal volume adjusted to maintain arterial P_{CO_2} at approximately 4.66 kPa, and prepared as reported previously.[4] Briefly, femoral and pulmonary arterial catheters were inserted for measurement of systemic and pulmonary haemodynamics and for sampling of arterial and mixed venous blood. Vascular pressures were recorded continuously and read at end-expiration. Cardiac output was measured using the thermodilution method with a fast-response thermistor catheter (93A-131-7.5F, Edwards, Santa Ana, CA, USA) and three injections of 10 ml of ice-cold saline delivered at the beginning of expiration. Cardiac output was controlled by inflating a balloon inserted in the inferior vena cava or by opening a femoral arteriovenous fistula to decrease or increase venous return, respectively.

After 200 ml of blood were obtained for clot formation, sodium heparin 100 u. kg^{-1} was given i.v. to prevent thrombus formation along the catheters. Normal saline was infused at a rate of 10 ml kg^{-1} h^{-1}. Temperature was maintained at 37–38 °C by a heating blanket. A left thoracotomy was performed at the fourth intercostal space. During thoracotomy, $F_{I_{O_2}}$ was increased to 0.6, and 3 cm H_2O of PEEP were applied to maintain adequate gas exchange and prevent atelectasis. Sufentanil boluses of 5–20 μg i.v. were given to provide appropriate analgesia. A non-constricting ultrasonic flow probe was positioned around the pulmonary artery, a manometer-tipped catheter inserted in the pulmonary artery via the RV outflow tract and a second manometer-tipped catheter placed in the RV via the right external jugular vein. Expired isoflurane was monitored with an Ultima respiratory gas analyser (SVi, Meda, Helsinki, Finland).

At the end of surgery, anaesthesia was maintained with the initial anaesthetic agent. After allowing 1 h for stabilization, the first five-point PAP/$\dot{Q}$ plot was generated by measuring PAP and $\dot{Q}$ with the arteriovenous bypass open (one point), then closed (one point), and after stepwise inflation of the inferior vena cava balloon (three points). $\dot{Q}$ and all intravascular pressures were recorded at each step. Arterial and mixed venous blood-gas tensions were measured at the highest and lowest $\dot{Q}$ values. Propofol or isoflurane was then discontinued and anaesthesia resumed with the alternate agent. One hour later, a second PAP/$\dot{Q}$ plot, PVZ data and associated measurements were obtained in a similar way. Embolic pulmonary hypertension was induced over 30 min by injecting blood clots into the jugular vein to reach a PAP of 40–50 mm Hg. Such embolic hypertension stabilizes at 30 mm Hg after 30 min and remains stable for hours.[6] The first three dogs embolized with 1.4% isoflurane anaesthesia died from irreversible cardiac failure before PAP stabilization and were excluded from the study.

In the following isoflurane-anaesthetized dogs, isoflurane was decreased to the lowest concentration compatible with adequate anaesthesia (less than 1%) during and just after embolization, and thereafter reset at 1.4%. After another 30-min period of haemodynamic stabilization, a third PAP/$\dot{Q}$ plot and PVZ data were collected. Anaesthesia was again resumed with the alternate agent, and a fourth PAP/$\dot{Q}$ plot and PVZ data were obtained 1 h later. Each of the nine remaining dogs thus received both anaesthetics before and after embolization. In order to assess the stability of the preparation, care was taken to recover initial post-embolic cardiovascular status and gas exchange variables after generation of each P/$\dot{Q}$ plot until the end of the experiment.

Instantaneous pressure and flow signals were digitized at a rate of 200 Hz, displayed on a monitor screen for visual inspection and stored in a computer. PAP/$\dot{Q}$ plots and PVZ data were analysed as reported previously.[4] Zero flow was adjusted to the end-diastolic plateau of the flow signal. Ultrasonic flow was scaled to the thermodilution value to compensate for ultrasonic underestimation of flow in large vessels,[4] and indexed to body surface area. From PVZ spectra were derived 0 Hz impedance (Z_0), which represents total pulmonary vascular resistance, characteristic impedance (Z_c), first harmonic modulus (Z_1) and phase (Ph_1). Z_c was calculated by averaging P/$\dot{Q}$ moduli between 2 and 10 Hz, and an index of wave reflection, the reflection coefficient (Rc) as $Rc=(Z_0-Z_c) / (Z_0+Z_c)$.[7] *W*tot was computed as the instantaneous pressure–flow product, and *W*osc as the difference between *W*tot and steady power (mean pressure–mean flow product).[7] d*P*/d*t*max was derived from the instantaneous RV pressure wave.

STATISTICAL ANALYSIS

Results are expressed as mean (SEM). Inspection of individual PAP/$\dot{Q}$ plots showed them to be linear and each plot was subjected to linear least square regression analysis. To obtain composite PAP/$\dot{Q}$ plots for each experimental situation, PAP values interpolated from individual regression analysis were averaged at 0.5-litre min^{-1} m^{-2} intervals from 2 to 3.5 litre min^{-1} m^{-2}. Data were analysed by repeated-measures analysis of variance. When the *F* ratio reached $P \leq 0.05$, comparisons were made using modified *t* tests, that is *t* tests calculated with the residual variance of analysis of variance.[8]

Results

MANIPULATIONS OF $\dot{Q}$

Manipulating venous return allowed variations in $\dot{Q}$ of 5.4–1.7 litre min^{-1} m^{-2} (table 1). PAP/$\dot{Q}$

Table 1 Blood-gas tensions and haemodynamic data in nine dogs anaesthetized with isoflurane or propofol, at baseline and after embolism, at the highest and lowest cardiac output. Values (mean (SEM)). HQ and LQ=high and low cardiac output, respectively; HR=heart rate; SAP=mean systemic arterial pressure; PAP=mean pulmonary arterial pressure; PAOP=mean pulmonary artery occluded pressure, RAP=mean right atrial pressure. $^*P<0.05$, $^{**}P<0.01$ embolism *vs* baseline at high Q; $\dagger P<0.05$, $\dagger\dagger P<0.01$ propofol *vs* isoflurane; $\ddagger P<0.05$, $\ddagger\ddagger P<0.01$ HQ *vs* LQ

		Baseline		Embolism	
	$\dot{Q}$	Isoflurane	Propofol	Isoflurane	Propofol
pH_a	HQ	7.38 (0.01)	7.41 (0.01)	7.36 (0.02)	7.36 (0.03)
	LQ	7.37 (0.02)	7.38 (0.02)	7.31 (0.02)	7.33 (0.02)
Pa_{O_2} (kPa)	HQ	18.6 (2.3)	18.9 (2.1)	13.6 (1.8)**	13.4 (1.9)**
	LQ	15.6 (2.8)‡‡	16.0 (2.3)‡‡	10.9 (1.6)‡‡	11.0 (1.5)‡‡
Pa_{CO_2} (kPa)	HQ	4.8 (0.1)	4 5 (0.1)	5.6 (0.4)**	5.6 (0.5)**
	LQ	4.5 (0.3)	4.5 (0.1)	5.6 (0.3)	5.7 (0.4)
$P\bar{v}_{O_2}$ (k.Pa)	HQ	6.1 (0.3)	6.4 (0.3)	5.7 (0.3)	6.0 (0.3)
	LQ	4.3 (0.1)‡‡	4.1 (0.1)‡‡	4.1 (0.1)‡‡	3.9 (0.1)‡‡
$\dot{Q}$ (litre min^{-1} m^{-2})	HQ	5.0 (0.7)	5.4 (0.6)	3.7 (0.3)**	3.9 (0.4)**
	LQ	1.8 (0.2)‡‡	1.9 (0.2) ‡‡	1.7 (0.2)‡‡	1.7 (0.2) ‡‡
HR (beat min^{-1})	HQ	137 (6)	149 (7)†	143 (12)	150 (8)
	LQ	131 (7)	157 (8)†	126 (10)‡‡	158 (12)†
SAP (mm Hg)	HQ	68 (4)	90 (6)††	63 (4)	79 (7)*††
	LQ	46 (1)‡‡	70 (5)‡‡	46 (2)‡‡	59 (4)‡‡
PAP (mm Hg)	HQ	19 (1)	20 (1)	27 (2)**	30 (2)**††
	LQ	14 (1)‡‡	13 (1)‡‡	21 (1)‡‡	23 (1)‡‡
PAOP (mm Hg)	HQ	9 (1)	9 (1)	13 (1)**	13 (2)**
	LQ	6 (1)‡‡	5 (1)‡‡	10 (1)‡	9 (1)‡
RAP (mm Hg)	HQ	8 (1)	6 (1)	10 (1)	8 (1)
	LQ	5 (1)‡‡	4 (1)‡‡	6 (1)‡‡	4 (1)‡‡

relationships appeared linear in all experimental situations with averaged correlation coefficients always greater than 0 9. As embolism was associated with a decrease in $\dot{Q}$ isoflow pulmonary vascular pressures comparisons were limited to $\dot{Q}$ values of 2–3.5 litre min^{-1} m^{-2} (fig. 1). Reducing $\dot{Q}$ was associated with lower arterial P_{O_2} (Pa_{O_2}) and mixed venous P_{O_2} ($P\bar{v}_{O_2}$), no change in arterial P_{CO_2} (Pa_{CO_2}) or in heart rate (HR) (except during isoflurane anaesthesia after embolism), and lower PAP, systemic arterial pressure (SAP), occluded PAP (PAOP) and right atrial pressure (RAP) (table 1).

PULMONARY EMBOLISM

Embolism was associated with a decrease in SAP (after propofol anaesthesia only), Pa_{O_2}, $\dot{Q}$ and increased Pa_{CO_2}, PAP and PAOP, while HR and RAP remained unchanged (table 1) There was an increase in PAP at all levels of $\dot{Q}$ (fig. 1). As determined at the same intermediate value of $\dot{Q}$ of 3 5 litre min^{-1} m^{-2}, embolism was associated with increased Z_0, Z_1, Rc, Ph_1 negativity and d*P*/d*t*max, a shift of the first minimum of impedance moduli to higher frequencies, decreased Z_c and *W*osc/*W*tot, without change in *W*tot (table 2, fig. 2).

COMPARISON OF ANAESTHETIC AGENTS

Before embolism, compared with propofol, isoflurane was associated with a lower HR, SAP and d*P*/d*t*max, but no change in blood-gas tensions, $\dot{Q}$, PAP, PAOP, RAP, Z_0, Z_1, Z_c, Rc, f_{min}, Ph_1, *W*tot or *W*osc/*W*tot (tables 1, 2). Before embolism, PAP/$\dot{Q}$ plots (fig. 1) and PVZ spectra (fig. 2) did not differ.

Table 2 Pulmonary vascular impedance and right ventricular function data in nine dogs anaesthetized with isoflurane or propofol alone, before and after embolism, at the same cardiac output (mean (SEM)). Z_0=0 Hz impedance modulus, Z_1=first harmonic impedance, Z_c=characteristic impedance; Rc=reflection coefficient; f_{min}=frequency of the first minimum; Ph_1=phase angle at the first harmonic; d*P*/d*t*max=maximum rate of increase in ventricular pressure; *W*tot=total hydraulic power; *W*osc=oscillatory power. $^*P<0.05$ embolism *vs* baseline; $\dagger P<0.05$ propofol *vs* isoflurane

	Baseline		Embolism	
	Isoflurane	Propofol	Isoflurane	Propofol
$\dot{Q}$ (litre min^{-1} m^{-2})	3.5 (0.2)	3.5 (0.2)	3.5 (0.3)	3.5 (0.2)
HR (Hz)	2.17 (0.09)	2.49 (0.13)†	2.15 (0.12)	2.45 (0.13)
Z_0 (dyn s cm^{-5})	316 (25)	340 (33)	509 (30)*	538 (41)*
Z_1 (dyn s cm^{-5})	67 (8)	65 (9)	77 (9)*	81 (10)*
Z_c (dyn s cm^{-5})	93 (11)	86 (10)	71 (11)*	73 (11)*
Rc (%)	55 (3)	59 (3)	76 (2)*	76 (2)*
f_{mm} (Hz)	3.0 (0.4)	2.8 (0.4)	4.4 (0.5)*	4.6 (0.6)*
Phl (rad)	0.10 (0.10)	0.06 (0.10)	−0.40 (0.04)	−0.40 (0.05)
d*P*/d*t*max (mm Hg s^{-1})	437 (57)	545 (69)†	528 (25)*	668 (88)*†
*W*tot (mW)	195 (34)	160 (26)	182 (20)	184 (28)
*W*osc/*W*tot (%)	23 (1)	22 (1)	21 (2)*	20 (1)*

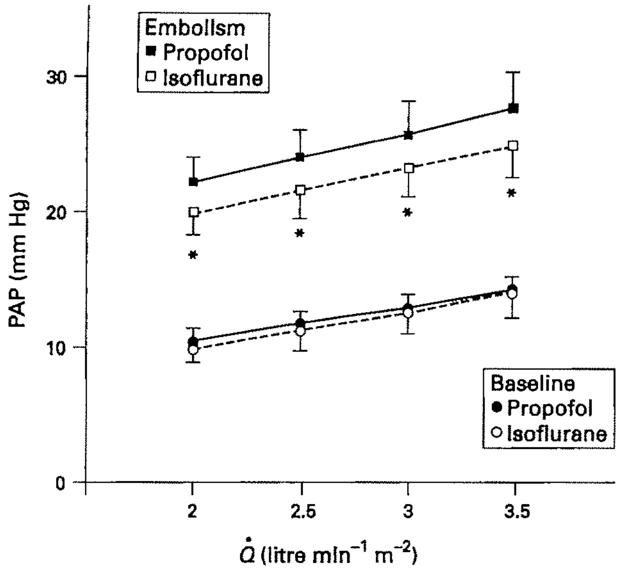

Figure 1 Pulmonary arterial pressure (PAP) *vs* cardiac output ($\dot{Q}$) at baseline and after pulmonary embolism in nine dogs anaesthetized with isoflurane or propofol (mean (SEM)). Embolism was associated with an increase in PAP at all levels of $\dot{Q}$ with both anaesthetics. Before embolism, PAP/$\dot{Q}$ plots did not differ during propofol or isoflurane anaesthesia. After embolism, isoflurane decreased PAP at all levels of $\dot{Q}$. $^{*}P<0.05$ isoflurane *vs* propofol after embolism.

After embolism, isoflurane was associated with a lower HR (except at high $\dot{Q}$), SAP, PAP, dP/dtmax, but no change in blood-gas tensions, $\dot{Q}$, PAOP, RAP, Z_0, Z_1, Z_c, Rc, f_{min}, Ph_1, *W*tot or *W*osc/*W*tot (tables 1, 2). After embolism, isoflurane was associated with a shift in PAP/$\dot{Q}$ plots to lower pressures at all levels of flow (fig. 1) but no difference in PVZ (fig. 2).

Discussion

We have demonstrated that in embolic pulmonary hypertension induced by autologous blood clots, pulmonary vascular tone decreased with isoflurane compared with propofol. However, this decrease was too modest to affect impedance, and RV vascular coupling during isoflurane may deteriorate because of decreased contractility.

ANAESTHETIC DOSE

Although it is difficult to compare inhaled and i.v. anaesthetic agents, we attempted to use equipotent doses of isoflurane and propofol on the basis of the available literature. In dogs, propofol at a rate of 18 mg kg^{-1} h^{-1} is associated with stable plasma concentrations of 5–7 μg ml^{-1}.[5] In acutely instrumented and unstimulated dogs, propofol at a rate of 12 mg kg^{-1} h^{-1} is the minimum rate compatible with adequate anaesthesia[9] and a rate of 30 mg kg^{-1} h^{-1} corresponds approximately to 1.5 MAC of isoflurane.[10] In this study, the depth of anaesthesia appeared comparable with propofol 18 mg kg^{-1} h^{-1} and 1.4 % end-tidal isoflurane (1 MAC for dogs) with regard to noxious stimuli such as reaction to skin incision. Baseline haemodynamic and blood-gas variables were similar with both drugs, with a somewhat lower heart rate and systemic arterial pressure during isoflurane anaesthesia.

NON-PULSATILE HAEMODYNAMICS

We evaluated pulmonary vascular tone by multipoint PAP/$\dot{Q}$ relationships, instead of isolated PVR calculations, to discriminate active from passive

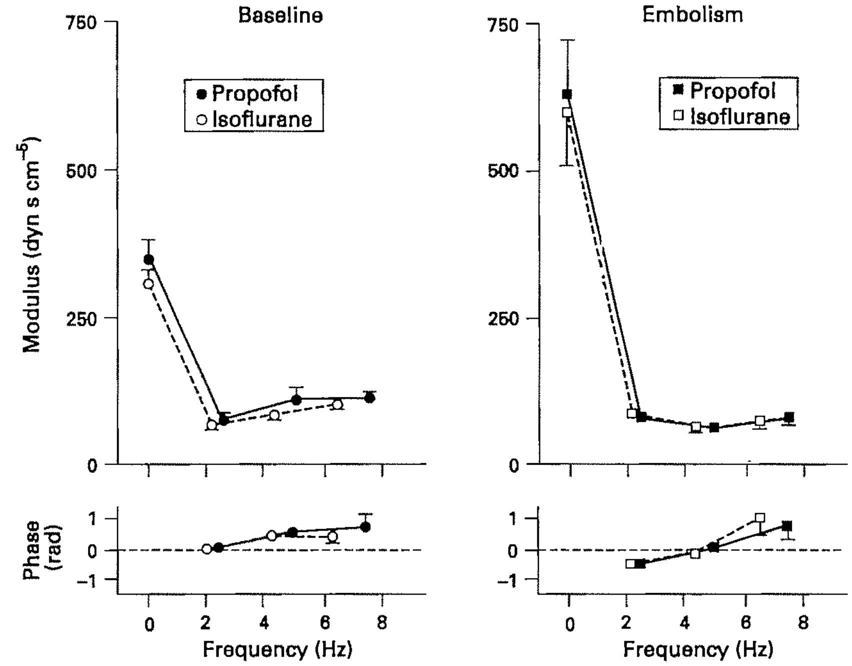

Figure 2 Pulmonary vascular impedance (PVZ) spectra, expressed as ratios of pulmonary artery pressure (PAP) and flow ($\dot{Q}$) moduli, and phase, both compared with frequency at identical intermediate cardiac output values (3.5 litre min^{-1} m^{-2}) before and after embolism (mean (SEM)). Pulmonary embolism increased 0 Hz impedance (Z_0), shifted the first minimum and maximum of PAP/$\dot{Q}$ to higher frequencies, decreased characteristic impedance (Z_c) and shifted the zero crossing of phase to higher frequencies (all $P<0.05$). PVZ spectra were not significantly different for isoflurane or propofol, at baseline or after embolism.

$\dot{Q}$-dependent changes in PAP.[11] We observed parallel upward shifts of PAP/$\dot{Q}$ relationships after embolism. According to the reference Starling resistor model, the extrapolated pressure intercept of PAP/$\dot{Q}$ plots represents the effective outflow pressure of the pulmonary circulation and the slope of PAP/$\dot{Q}$ plots incremental pulmonary vascular resistance.[11] When the extrapolated pressure intercept of PAP/$\dot{Q}$ plots is higher than left atrial pressure (estimated by PAOP), as occurs in experimental pulmonary embolism, this may be explained by the existence of increased vascular closing pressure making left atrial pressure an irrelevant backward pressure in respect of flow.[6 12] However, a distensible vessel model has been reported recently which explains parallel shifts of PAP/$\dot{Q}$ plots to higher pressures after embolism without having to invoke vascular closure.[11 13] Therefore, we did not speculate on the functional significance of slopes and extrapolated pressure intercepts of PAP/$\dot{Q}$ plots in this study. However, our results showed that embolism increased PVR in a $\dot{Q}$-independent manner, and that this change was slightly reversed with isoflurane.

Previous studies that reported minimal or no pulmonary vasodilating effect of isoflurane in various experimental settings[2 3 14 15] included background i.v. anaesthesia with barbiturates. Pentobarbitone anaesthesia alone does not affect PAP/$\dot{Q}$ relationships in hyperoxic sheep lungs[16] or in normoxic intact dogs,[17] but alters autonomic nervous regulation of the pulmonary circulation.[17] Barbiturates may reduce HPV by 14–28% at clinically relevant doses in isolated sheep lungs,[16] but it is not known if this can be extrapolated to intact animals. How background anaesthesia might interfere with the pulmonary vascular effects of isoflurane is uncertain. Comparing isoflurane alone with propofol alone, we reported previously a decrease in pulmonary vascular tone in hyperoxic and hypoxic dogs.[4] In that study, Pa_{O_2} at an FI_{O_2} of 0.4 was consistently lower than in the present experiments, suggesting the presence of low ventilation/perfusion areas, probably related to post-thoracotomy atelectasis, inducing some local hypoxic vasoconstriction that was counteracted with isoflurane. In our study, Pa_{O_2} was preserved better suggesting no lung abnormalities. Baseline PAP/$\dot{Q}$ plots during isoflurane and propofol anaesthesia did not differ, suggesting that isoflurane had no effect on the normally low pulmonary vascular tone. These results concur with those of Lennon and Murray who found similar PAP/$\dot{Q}$ plots in chronically instrumented dogs in the conscious state and during isoflurane anaesthesia.[18]

The pulmonary vascular effects of propofol are not well documented. In pentobarbitone-anaesthetized dogs, propofol did not affect hyperoxic or hypoxic PAP/$\dot{Q}$ plots, before or after cyclooxygenase inhibition.[5] However, in isolated rat aorta and pulmonary arteries, propofol exerted vasorelaxant effects, mediated partly via the cyclooxygenase pathway.[19] Compared with the conscious state, PAP/$\dot{Q}$ plots during propofol anaesthesia might thus be shifted slightly to lower pressures. After embolism, PAP/$\dot{Q}$ plots were shifted to lower pressures with isoflurane compared with propofol. However, this effect was small (a few mm Hg) and equivalent to the vasodilatation observed after hydralazine, isoproterenol and nitroprusside,[6 12] confirming that the functional vasoactive component of increased PVR in embolic pulmonary hypertension is modest and in this case better preserved with propofol than with isoflurane.

PULSATILE HAEMODYNAMICS

In the pulmonary circulation, $\dot{W}$osc is a relatively important fraction of RV external $\dot{W}$tot, which is determined by dynamic interplay between PVR, elastance and wave reflections.[7 11] To evaluate all of the forces that oppose RV ejection, the natural pulsatility of the pulmonary circulation must be taken into account. This is possible by analysis of pressure and flow waves in the frequency domain to calculate PVZ.[7 11] In the present experiments, PVZ spectra before embolism had a classical pattern: a relatively high Z_0 followed by a steep decrease to a minimum of 2–4 Hz, small fluctuations at higher frequencies and a slightly negative phase at lower frequencies.[4 20 21] Milnor, Bergel and Bargainer found no difference in PVZ spectra between awake and halothane-anaesthetized dogs.[21] In our dogs, PVZ spectra were comparable with isoflurane and propofol at baseline. Pulmonary embolism induced by autologous blood clots[22] or 150–200 µm glass beads[20] has been reported to increase Z_0, Z_1, Rc and phase angle negativity, indicating an increase in total pulmonary vascular resistance (Z_0), pulmonary arterial elastance (Z_1) and wave reflection (Rc and phase negativity),[7] and a decrease in Z_c.[20 22] Our results concur. A decrease in Z_c in embolic pulmonary hypertension can be explained by dilatation of the pulmonary arterial tree.[20 22] The characteristic impedance Z_c is the ratio of inertance over compliance of the proximal vessels and varies directly with the elastic modulus of the vessel and indirectly with its cross-sectional area.[7] In our dogs, although isoflow PVR values (evaluated by P/$\dot{Q}$ plots) were lower with isoflurane compared with propofol after embolism, PVZ spectra were not affected differently by anaesthesia. In canine blood clot embolic pulmonary hypertension, Z_c or pulmonary arterial compliance did not change after meclofenamate, ketanserin, atropine or vagotomy.[22] It is thus possible that the only component of PVZ amenable to active neurohumoral control in acute embolic pulmonary hypertension is distal PVR and that isoflurane and propofol might not act differently at conduit (proximal) pulmonary arteries in pulmonary embolism.

RIGHT VENTRICULO-VASCULAR INTERACTION

In the present experiments, baseline RV pressures, $\dot{W}$tot and $\dot{W}$osc/$\dot{W}$tot were comparable with those reported elsewhere.[21 22] Embolism did not affect $\dot{W}$tot and decreased slightly $\dot{W}$osc/$\dot{W}$tot. This also concurs with previous observations.[22] The absence of change in $\dot{W}$tot after embolism may be explained by an increase in wave reflection. This causes pressure and flow waves to become out of phase so that their instantaneous product decreases, as does *W*osc/*W*tot.[22] The latter is beneficial as *W*osc is dissipated in the pulmonary vascular bed and wasteful in terms of blood motion.[7] *W*osc/*W*tot is decreased by an increase in heart rate or a decrease in *Z*c, or both.[21] In this study, since heart rate did not change with embolism, the lower *W*osc/*W*tot was probably related to the decrease in Z_c. At a $\dot{Q}$ value of 3.5 litre $\text{min}^{-1}\ \text{m}^{-2}$, d*P*/d*t*max, a load-dependent index of contractility,[23] was increased after embolism. This allowed only a moderate decrease in $\dot{Q}$ in the face of an increased afterload. At comparable preload and afterload, as evaluated by RAP and PVZ, respectively, d*P*/d*t*max was lower with isoflurane than with propofol. After embolism, lower contractility and lower systemic arterial pressure with isoflurane led to occasional acute right heart failure probably related to impairment of myocardial perfusion, as a consequence of decreased coronary perfusion pressure.[23] Observations made *in vitro* on the isolated ferret myocardium have also demonstrated more important negative inotropic effects of isoflurane compared with propofol at clinically relevant doses.[24 25]

Thus in canine embolic pulmonary hypertension, compared with propofol, isoflurane caused deterioration in RV arterial coupling by a decrease in myocardial contractility, whereas RV afterload evaluated by PVZ was not decreased, despite a small reduction in pulmonary vascular tone evaluated by PAP/$\dot{Q}$ plots.

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Extra-pulmonary effects of inhaled nitric oxide in swine with and without phenylephrine

E. TRONCY, M. FRANCŒUR, I. SALAZKIN, F. YANG, M. CHARBONNEAU, G. LECLERC, P. VINAY AND G. BLAISE

Summary

We have compared the effects of inhaled nitric oxide (iNO) and i.v. nitroglycerin (ivGTN) on the haemodynamic response to phenylephrine-induced hypertension (PEHT) in anaesthetized pigs. PEHT did not change either pulmonary vascular resistance or gas exchange throughout all experiments. Both treatments lowered pulmonary arterial pressure to the same extent (−12.4% iNO; −13.7% ivGTN) and passively via an effect on left atrial pressure (−26.3% iNO; −31.4% ivGTN). Both treatments failed to reverse the decrease in renal blood flow (RBFc) induced by PEHT, but both increased urinary flow (UF) (+128% iNO; +148% ivGTN). IvGTN significantly increased plasma concentrations of nitrite and nitrate during (+22.7% arterial blood; +26.2% venous blood) and beyond the period of infusion (iNO: +6.4% and +4.9%, respectively). In four control pigs (no PEHT), iNO markedly increased RBFc (+109%), glomerular filtration rate (+72.5%) and UF (+68.7%). We conclude that iNO may have direct cardiac and renal effects, probably via intervention of NO carrier forms such as *S*-nitroso compounds. (*Br. J. Anaesth.* 1997; **79**: 631–640).

Key words

Gases non-anaesthetic, nitric oxide. Pharmacology, nitric oxide. Pharmacology, nitroglycerin. Sympathetic nervous system, phenylephrine. Pig. Kidney, function. Kidney, diuresis.

I.v. endothelium-independent nitrovasodilators such as sodium nitroprusside and nitroglycerin (ivGTN) produce their vasodilator effects by providing nitric oxide.[1] In contrast with i.v. medication, inhaled nitric oxide (iNO) is used commonly as a selective pulmonary vasodilator in experimental[2] and clinical[3] conditions. Inhaled NO is "microselective" in that it dilates only vessels directly adjacent to the alveolar units being ventilated. Therefore, in a hypoxaemic patient, iNO may improve oxygenation by improving ventilation/perfusion matching with redistribution of blood flow from unventilated shunted areas to ventilated but underperfused areas.[4] Some authors also explain the improved oxygenation with iNO by the fact that it produces local bronchodilation,[2 4] decreases vascular permeability and the appearance of pressure-driven pulmonary oedema,[4] and exerts a platelet anti-aggregating effect.[2]

A swine model has been used in the past to study the treatment of experimental pulmonary hypertension induced by hypoxia,[5] a thromboxane analogue,[6] oleic acid-induced ARDS[7] or sepsis.[2 4] Phenylephrine is a sympathomimetic amine commonly used in *in vitro* studies of the L-arginine:NO pathway[8] or to counteract clinical hypotension.[9] We have developed a phenylephrine-induced hypertension (PEHT) model in anaesthetized pigs. We wished to test the hypothesis that iNO does not affect the systemic circulation. Accordingly, we compared the effects of iNO and ivGTN on pulmonary and systemic haemodynamics and gas exchange, in addition to plasma and urinary concentrations of nitrite (NO_2^-) and nitrate (NO_3^-), stable metabolites of nitrogen oxides and related species (NO_xs), that is pNO_x^- and uNO_x^-, respectively. In order to evaluate potential extra-pulmonary effects of iNO, we have compared the effects of iNO and ivGTN on diuresis and renal haemodynamics in pigs in the presence or absence of PEHT.

Materials and methods

This study was approved by the Institutional Research and Animal Welfare Committee. The animals were treated according to the Canadian Council on Animal Care guidelines. We studied 28 female pigs, mean weight 22.84 (SEM 0.27) kg.

The pigs were premedicated with azaperone 2 mg kg^{-1} i.m., ketamine 15 mg kg^{-1} i.m. and atropine 4 μg kg^{-1} i.m. After induction of anaesthesia with fentanyl 5 μg kg^{-1} i.v. and pentobarbitone 6.5 mg kg^{-1} i.v., the trachea was intubated and the lungs ventilated using a volume-controlled ventilator (Ventilator 7200 AE, Puritan Bennett, Carlsbad,

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ERIC TRONCY, DVM, MSC, MARTIN FRANCŒUR, RRT, IGOR SALAZKIN, MD, FAN YANG, MD, GILBERT BLAISE, MD (Anaesthesia Laboratory and Department of Anaesthesia); MARC CHARBONNEAU, MD, GUY LECLERC, MD, PATRICK VINAY, MD, PHD (Department of Medicine); Centre Hospitalier de l'Université de Montréal-Pavillon Notre-Dame, 1560 Sherbrooke Street East, Québec, Canada H2L 4M1. Accepted for publication: June 25, 1997.

CA, USA). Tidal volume was set at 15 ml kg^{-1}, $F_{I_{O_2}}$ at 0.30 (Oxygen Monitor 5590, Hudson RCI, Temecula, CA, USA) and ventilatory frequency adjusted to maintain the partial pressure of arterial carbon dioxide (Pa_{CO_2}) at 4.6–6.0 kPa (Blood gases analyser IL 1620, Coulter Electronics Ltd, Ville Saint-Laurent, Qc, Canada). Anaesthesia was maintained with continuous infusion of fentanyl 3.8 μg kg^{-1} h^{-1} and pentobarbitone 9.8 mg kg^{-1} h^{-1}. Neuromuscular block was produced with a mixture of tubocurarine 0.2 mg kg^{-1} h^{-1} and pancuronium 0.15 mg kg^{-1} h^{-1}. Lactated Ringer's solution was infused at a rate of 15 ml kg^{-1} h^{-1} to meet maintenance needs during open-chest surgery.

After placing the electrocardiographic leads, we inserted an arterial pressure catheter (carotid artery), two venous infusion cannulae (external jugular vein, auricular vein), a pulmonary artery thermodilution catheter (for cardiac output), a core temperature probe and central venous catheter. Median sternotomy was performed, the pericardium opened and two catheters (12-gauge) inserted, one into the main pulmonary artery and the other into the left atrial appendage for pressure monitoring in addition to arterial and venous blood sampling for blood-gas analysis. The pericardium and chest wall were closed with sutures and metallic wires. Via a laparotomy, the left renal vein (renal venous blood sampling site) and both ureters were catheterized, and the left ovarian vein was ligated because of drainage into the renal vein. After instrumentation, 45 min were allowed to elapse to obtain a stable physiological state.

Each experiment was divided into four stages (I–IV) of 20 min (table 1). Animals were enrolled in the experiments in random order.

Control arm. In control studies we evaluated the effect of time (experiment A), PEHT alone (experiment B) and iNO alone (experiment C).

Experimental arm. The four stages in the experiments were: (I) baseline measurements, (II) induction of PEHT by continuous infusion of phenylephrine diluted in saline (mean 14.68 (SEM 1.36) μg kg^{-1} min^{-1}), (III) intervention to treat PEHT with an infusion of ivGTN (experiment D) or 40 ppm of iNO (experiment E), and (IV) a recovery period where both the hypertensive stimulus and treatment were discontinued.

ADMINISTRATION OF IVGTN

The dose of ivGTN (Nitroject, Omega Laboratories Ltd, Montréal, Qc, Canada) was started at 10 μg kg^{-1} min^{-1} and increased progressively (3-min interval) to reduce mean pulmonary arterial pressure to the level observed after iNO. The period of measurement (stage III) was then started. The mean final dose of ivGTN used in experiment D was 92.43 (SEM 13.45) μg kg^{-1} min^{-1}.

ADMINISTRATION OF INO

A mixture of NO–N_2 972 ppm (Cylinder NO 972 ppm, <5 ppm of NO_2, Vitalaire Canada, Montréal, Qc, Canada) was injected cyclically into the inspiratory limb of the ventilator system using a method developed in our institution.[10] Concentrations of gaseous NO and NO_xs were monitored continuously using a chemiluminescence analyser (CLD700AL NO/NO_x analyser, Ecophysics Tecan AG, Dürten, Switzerland). Based on our previous work,[5 6] we chose to study the effects of iNO 40 ppm. This dose was shown in several studies[3–7] to have a significant pulmonary vasodilator effect while ensuring an inspired fraction of NO_2 below 1 ppm with our system.[10]

RENAL MONITORING

Thirty minutes before the beginning of baseline measurements (stage I), a bolus of inulin 2 g and para-amino-hippuric acid (PAH) 2 g dissolved in 50 ml of glucose were administered, immediately followed by an infusion of inulin 2 g and PAH 4 g dissolved in 1000 ml of glucose at a constant rate of 1 ml min^{-1}. Blood samples (4 ml) were obtained simultaneously from the left renal vein and carotid artery in order to measure packed cell volume (PCV), PAH and inulin concentrations, in addition to arterial and venous pNO_x^- concentrations. Blood samples were collected at the beginning of stage I and at the end of each 20-min period. Urine was collected separately in graduated cylinders from both ureters at 5-min interval during the whole procedure to measure urinary flow (UF), PAH and inulin concentrations, and uNO_x^-. The concentration of PAH in both urine and blood was measured using the technique described by Bratton and Marshall.[11] Renal plasma flow (RPF) was taken as PAH clearance ($Cl_{PAH}=C_u \times (UF/C_a)$, where C_u=PAH concentration in urine and C_a=PAH concentration in arterial blood plasma). Renal plasma flow was corrected (RPFc) for PAH extraction coefficient

Table 1 Study design. *No intervention. †PE=Phenylephrine infusion at mean 15.75 (SEM 0.85) μg kg^{-1} min^{-1}; ‡PE=phenylephrine infusion at 14.68 (1.36) μg kg^{-1} min^{-1}; iNO=inhaled nitric oxide 40 ppm; ivGTN=nitroglycerine infusion at 92.43 (13.45) μg kg^{-1} min^{-1}

		Stage and time				
Arm	Protocol	I 30–50′	II 50–70′	III 70–90′	IV 90–110′	Sample size
Control	A	Nil*	Nil	Nil	Nil	n=4
	B	Nil	PE†	PE†	Nil	n=4
	C	Nil	iNO	iNO	Nil	n=4
Experimental	D	Nil	PE‡	PE‡-ivGTN	Nil	n=8
	E	Nil	PE‡	PE‡-iNO	Nil	n=8

($E_{PAH}=(C_a-C_v)/C_a$, where C_v=PAH concentration in renal vein blood plasma), and renal blood flow corrected for PAH extraction (RBFc) was taken as RPFc/(1−PCV). Because PAH acetylation was observed with some pigs, RBFc was calculated for each 5-min interval using PAH and inulin clearances and extractions. Inulin concentration was measured by an anthrone colorometric technique,[12] and whole kidney glomerular filtration rate (GFR) was calculated for each 5-min interval by the standard clearance formula.

MEASUREMENTS OF PNO_x^- AND UNO_x^-

Plasma samples obtained by centrifugation were diluted 10-fold with distilled water and deproteinized by adding 5% volume of zinc sulphate to a final concentration of 15 g litre^{-1}.[13] After centrifugation at 1000×*g* for 15 min at room temperature, 100 μl of supernatant were applied to a microreaction purge vessel chamber (270B NO analyser, Sievers Research Inc, Boulder, CO, USA) equipped with a temperature regulator and a condenser, which allowed direct introduction of prepared plasma and urine samples into the reducing solution. pNO_x^- and uNO_x^- concentrations were measured by conversion to NO using hot acidic vanadium (III) chloride. NO was eluted in a stream of nitrogen and detected by an ozone-induced chemiluminescence reaction. The NO/NO_x analyser was connected directly to a data acquisition system (Mac Lab, Lamont Scientific Ltd., Downsview, Ont, Canada). Each sample was analysed in duplicate and measured once at the end of each 20-min period, as described previously.[13]

CARDIORESPIRATORY VARIABLES

Systolic (SAP), mean (MAP) and diastolic (DAP) systemic arterial pressures, mean pulmonary arterial pressure (PAP), left atrial pressure (LAP), central venous pressure (CVP), heart rate (HR) and cardiac output (CO; 5 ml of cold normal saline were injected in triplicate for each measurement) were recorded every 5 min in each period. Arterial and mixed venous blood-gas tensions were measured once at the end of each 20-min period.

DATA ANALYSIS

In the control arm, the sample size was $n=4$ for each experiment (table 1). In the experimental arm, the sample size was $n=8$ for each experiment. Half of the pigs in experiments D and E were used to evaluate renal effects and the other half to measure pNO_x^- and uNO_x^- concentrations.

Data distribution of each variable was Gaussian. For each stage, mean values of four measurements (obtained every 5 min) or a single measurement (obtained only once during each stage) were chosen as the values for the period. Pulmonary (PVR) and systemic (SVR) vascular resistances were calculated using standard formulae. All values are reported as mean (SEM) for each variable in each stage (I–IV) of the experiments.

Data were analysed using SuperANOVA (V 1.11, Abacus Concepts Inc. 1989/1991, Berkeley, CA, USA) and SAS (Statistical Analysis System V6.11 for Windows 95, SAS Institute Inc. 1995, Cary, NC, USA) software.

For each experiment, the effect of stage was evaluated with the one-factor repeated measures analysis of variance (F-ANOVA) and, when necessary, multiple comparisons were made using Fisher's protected least significant difference (LSD_F) test.

Between the five experiments, for the difference between two stages (e.g. stages-difference

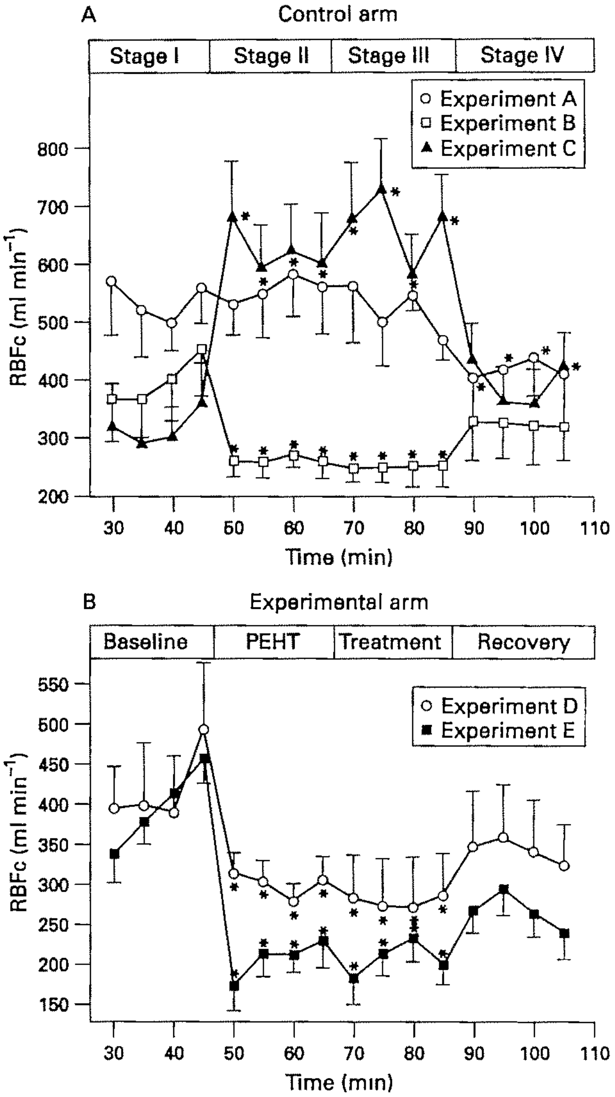

Figure 1 Variation in renal blood flow corrected for PAH extraction (RBFc). A. Control arm: mean (SEM) values for RBFc for each sampling time in each stage (I–IV) for experiment A (no intervention during the four stages), experiment B (infusion of phenylephrine 15.75 (0.85) μg kg^{-1} min^{-1} during stages II and III), and experiment C (iNO 40 ppm during stages II and III). RBFc decreased with time in experiment A. Infusion of phenylephrine significantly reduced RBFc while iNO considerably increased RBFc. *Significant difference for F-ANOVA (P<0.05) and for the LSD_F test of the stage compared with stage I (P<0.008). B: Experimental arm. mean (SEM) values for RBFc for each sampling time in each stage (I–IV) for experiment D (PEHT+ivGTN treatment) and experiment E (PEHT+iNO treatment). Infusion of phenylephrine significantly reduced RBFc and nitrergic treatments failed to reverse the decrease.*Significant difference for F-ANOVA (P<0.05) and for the LSD_F test of the stage compared with stage I (P<0.008). (See text for further details.)

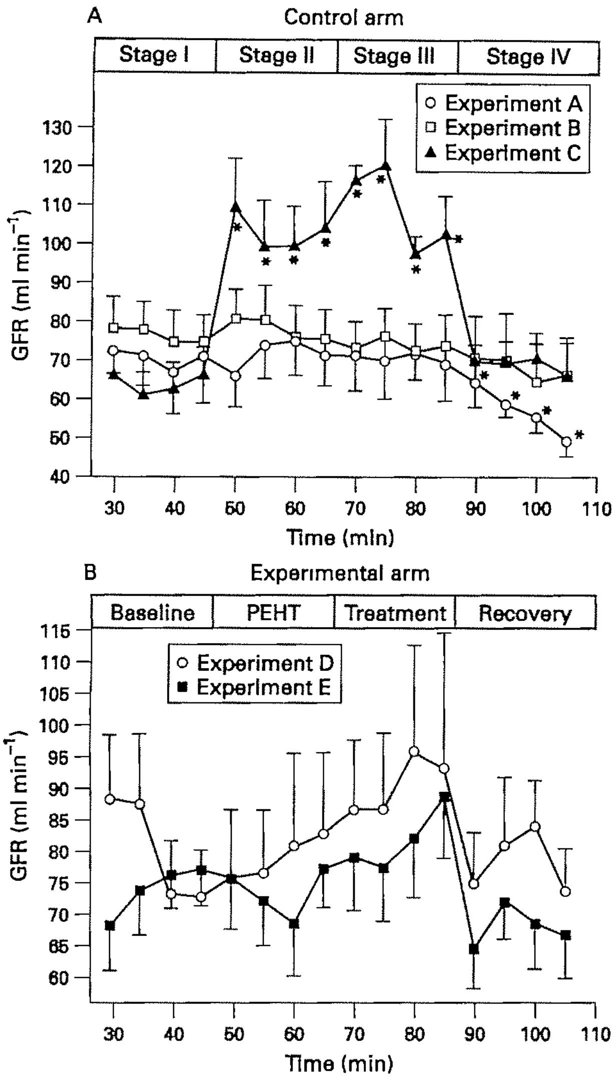

Figure 2 Variation in glomerular filtration rate (GFR). A: Control arm: mean (SEM) values for GFR for each sampling time in each stage (I–IV) for experiment A (no intervention during the four stages), experiment B (infusion of phenylephrine 15.75 (0.85) $\mu g\ kg^{-1}\ min^{-1}$ during stages II and III), and experiment C (iNO 40 ppm during stages II and III). GFR decreased with time in experiment A. Infusion of phenylephrine had no effect on GFR while iNO considerably increased GFR. *Significant difference for F-ANOVA ($P<0.05$) and for the LSD_F test of the stage compared with stage I ($P<0.008$). B: Experimental arm: mean (SEM) values for GFR for each sampling time in each stage (I–IV) for experiment D (PEHT+ivGTN treatment) and experiment E (PEHT+iNO treatment). Infusion of phenylephrine and nitrergic treatments did not modify GFR. (See text for further details.)

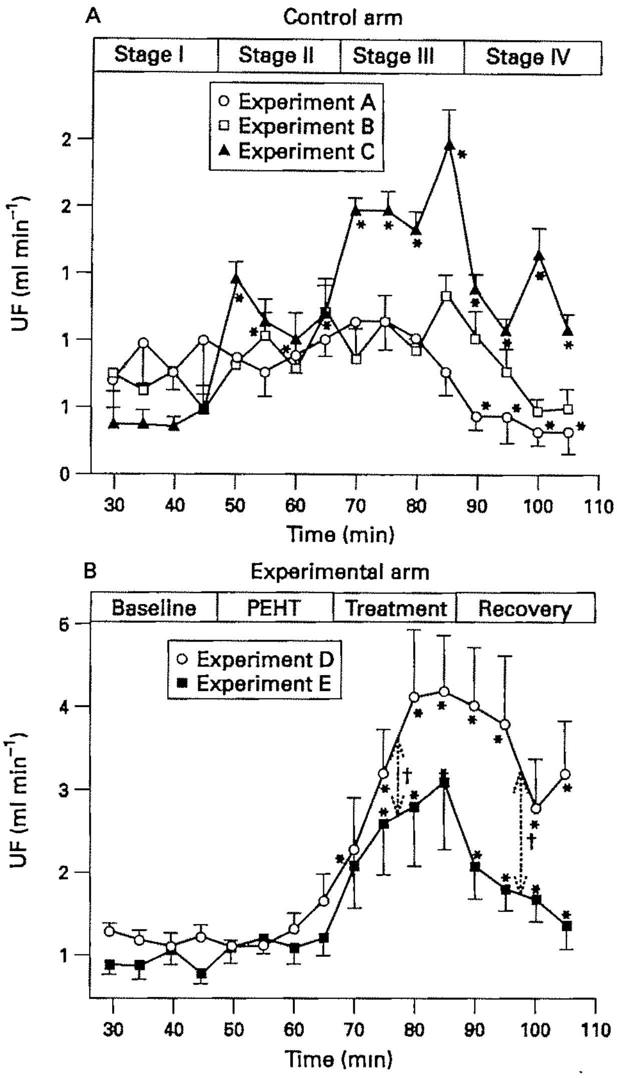

Figure 3 Variation in urinary flow (UF). A: Control arm: mean (SEM) values for UF for each sampling time in each stage (I–IV) for experiment A (no intervention during the four stages), experiment B (infusion of phenylephrine 15.75 (0.85) $\mu g\ kg^{-1}\ min^{-1}$ during stages II and III), and experiment C (iNO 40 ppm during stages II and III). UF decreased with time in experiment A. Infusion of phenylephrine had no effect on UF while iNO considerably increased UF. *Significant difference for F-ANOVA ($P<0.05$) and for the LSD_F test of the stage compared with stage I ($P<0.008$). B: Experimental arm: mean (SEM) values for UF for each sampling time in each stage (I–IV) for experiment D (PEHT+ivGTN treatment) and experiment E (PEHT+iNO treatment). Infusion of phenylephrine did not modify UF and both nitrergic treatments significantly increased UF, ivGTN more than iNO. *Significant difference for F-ANOVA ($P<0.05$) and for the LSD_F test of the stage compared with stage I ($P<0.008$). †Significant difference between groups for W-ANOVA ($P<0.05$) and for the LSD_W test ($P<0.005$) on the difference (III–II) and (IV–III). (See text for further details.)

(III–I)=between stages III and I), one-way analysis of variance (W-ANOVA) was used and multiple comparisons were made using Fisher's protected least significant difference (LSD_W) test.

$P<0.05$ was considered significant, except for multiple comparisons where the global significance level of 0.05 was adjusted for the number of null hypotheses tested ($P<0.008$ for multiple comparisons within group LSD_F and $P<0.005$ for multiple comparisons between the five groups LSD_W).

Results

For each experiment, the cardiovascular, renal and metabolic (pNO_x^-, uNO_x^-) effects observed during each stage are presented.

CONTROL ARM

In experiment A on the effect of time, there was no change in the measured variables, except for a decrease in renal haemodynamics and diuresis: stage IV was different from the three preceding periods for RBFc (−22.9%; fig. 1A), GFR (−20.8%; fig. 2A) and UF (−19.5%, fig. 3A).

Table 2 Effects of phenylephrine (PEHT) and its treatment by inhaled NO (iNO) or i.v. nitroglycerin (ivGTN) on pulmonary and systemic haemodynamic variables (mean (SEM) in anaesthetized pigs. [III–II]=Mean (SEM) values of the percentage variation between stages III (treatment) and II (PEHT). *P value <α; †P value of the one-factor repeated measures analysis of variance for the within-group analysis on the four periods was not significant. P_1=P value of Fisher's protected LSD_F test for comparison of stages II and III within group (α=0.008); P_2=P value of Fisher's protected LSD_W test for comparison of the difference [III–II] between groups (α=0.005)

		Baseline (I)	PEHT (II)	Treatment (III)	[III–II] (%)	Recovery (IV)	P_1
PAP (mm Hg)	iNO	22 (0.97)	29.1 (1.17)	25.5 (1.06)	−12.4 (0.81)	23.06 (1.1)	0.0001*
	ivGTN	21.5 (1.23)	29.1 (1.52)	25.1 (0.64)	−13.7 (1.34)	23.8 (0.83)	0 001*
					P_2=0.51		
PVR (dyn s cm^{-5})	iNO	382.9 (16)	341.8 (23.37)	357.3 (18.27)	+4.5 (3.63)	416.3 (20)	ns†
	ivGTN	309.4 (17.3)	313.7 (23)	309.3 (20.7)	−1.4 (2.82)	336.5 (29.5)	ns
					P_2=0.92		
MAP (mm Hg)	iNO	104.9 (7.8)	172.5 (4.56)	161.5 (4.35)	−6.3 (3.07)	100.4 (5.32)	0.004*
	ivGTN	89.8 (3.4)	160.1 (1.52)	97.1 (4.84)	−39.4 (4.52)	84.5 (2.8)	0.0001*
					P_2=0.00001*		
SVR (dyn s cm^{-5})	iNO	3020.8 (149.1)	4924.3 (217.2)	4494.3 (159.2)	−8.7 (7.7)	3133 5 (123)	0.068
	ivGTN	2318.9 (85.7)	4480.3 (253)	2263.9 (146.8)	−49.3 (9.96)	2292.6 (136)	0.00001*
					P_2=0.001*		
SAP (mm Hg)	iNO	116.2 (6.96)	199.7 (4.7)	178.2 (4.63)	−10.8 (2.22)	111.6 (3.4)	0.0001*
	ivGTN	109.4 (3.64)	196.9 (2.54)	122.2 (5.5)	−37.9 (4.77)	104.6 (3.2)	0.0001*
					P_2=0.000001*		
DAP (mm Hg)	iNO	91.31 (5.3)	147.6 (4.87)	140.5 (4.56)	−4.8 (1.8)	84.55 (4)	0.04
	ivGTN	75.82 (4.92)	138.5 (5.4)	79.6 (3.92)	−42.5 (5.55)	67.96 (3.2)	0.0001*
					P_2=0.000001*		
LAP (mm Hg)	iNO	9.06 (0.9)	17.1 (1.1)	12.6 (1.27)	−26.3 (3.78)	10.06 (1.07)	0.0001*
	ivGTN	10.5 (1.13)	18.8 (1.52)	12.9 (0.46)	−31.4 (6.1)	12.43 (0.72)	0.0001*
					P_2=0.1		
CVP (mm Hg)	iNO	5.72 (0.4)	9.9 (0.92)	8 (0.64)	−19.1 (2.76)	6.14 (0.5)	0.0001*
	ivGTN	7.7 (0.37)	10.5 (0.46)	7.8 (0.39)	−25.7 (3.43)	7.86 (0 31)	0.0001*
					P_2=0 09		
HR (beat min^{-1})	iNO	122.6 (7.51)	120.6 (7.1)	132.2 (9.36)	+9.06 (2 6)	129.4 (5 6)	ns
	ivGTN	132.43 (9)	141.3 (10.3)	158.1 (9.75)	+11.9 (3.85)	144.6 (8)	ns
					P_2=0.1		
CO (litre min^{-1})	iNO	2.73 (0.18)	2.76 (0.18)	2.81 (0.14)	+1.8 (2.05)	2.47 (0.16)	ns
	ivGTN	2.87 (0.15)	2.95 (0.35)	3.1 (0.28)	+5.1 (2.76)	2.86 (0.26)	ns
					P_2=0.37		

Table 3 Plasma nitrite and nitrate (pNO_x^-) concentrations (mean (SEM)) during phenylephrine-induced hypertension (PEHT), and its treatment with superimposed inhaled NO (iNO) or i.v. nitroglycerin (ivGTN) in anaesthetized pigs. There was no difference between arterial and venous pNO_x^- values. *P value <α. P_1=P value of the one-factor repeated measures analysis of variance for the within-group analysis on the four periods (α=0.05); P_2=P value of Fisher's protected LSD_F test for multiple comparison of stages within group (α=0.008). P_3=P value of Fisher's protected LSD_W test for comparison of the stages-difference between experiments D and E (α=0.005)

		Baseline (I)	[II–I]	PEHT (II)	[III–II]	Treatment (III)	[IV–III]	Recovery (IV)	[IV–I]	P_1
Arterial pNO_x^-	iNO	86.4 (2.1)		90.6 (1.3)		96.4 (2.7)		82.7 (2.6)		0.002*
(µmol litre^{-1})	P_2		0.16		0.057		0.0001*		0.21	
	ivGTN	98.7 (8.3)		102 (11)		124.6 (12)		122 (9.5)		0.004*
	P_2		0.9		0.003*		0.9		0.001*	
	P_3		0.71		0.002*		0.0048*		0.001*	
Venous pNO_x^-	iNO	93 (6.29)		101 (7.1)		105.9 (4.1)		90.1 (3.5)		0.04*
(µmol litre^{-1})	P_2		0.39		0.63		0.004*		0.76	
	ivGTN	85.5 (6.9)		92.5 (10)		117 (11.2)		113 (10)		0.02*
	P_2		0.78		0.004*		0.89		0.001*	
	P_3		0.17		0.002*		0.004*		0.003*	

During experiment B, phenylephrine significantly increased PAP by 40% (LSD_F comparison of stage II with stage I: P=0.0001), but PVR remained unchanged (F-ANOVA: P=0.42). PEHT significantly increased MAP and SVR: +65.9% and +64.5%, respectively. LAP and CVP exhibited similar changes: +67.9% and +49%, respectively. Phenylephrine had no effect on HR or CO (F-ANOVA, P=0.17 and P=0.33, respectively). The haemodynamic changes were stable during stage III. Compared with stage I, phenylephrine induced a similar decrease in RBFc for stage II (−34%, LSD_F: P=0.001) (fig. 1A) and III (−37%, LSD_F: P=0.001) (fig. 1A) but other renal variables remained unchanged (figs 2A and 3A). The vasoconstrictor did not significantly modify arterial (92.6 (4) to 96 (5.1) µmol litre^{-1}) or venous (89.8 (5.5) to 94.1 (8.3) µmol litre^{-1}) pNO_x^- or uNO_x^- (988.2 (73.4) to 1132.4 (102.6) µmol litre^{-1}) concentrations.

In experiment C, iNO alone did not significantly alter cardiorespiratory variables. However, renal function was affected: RBFc increased by +94% (LSD_F: P=0.0046) (fig. 1A), GFR by +63% (LSD_F: P=0.0001) (fig. 2A) and UF by +34% (LSD_F: P=0.006) (fig. 3A) during stage II; the changes in the three variables remained constant during stage III (+109%, +72.5% and +68.7%, respectively) (figs 1A–3A). UF remained high during stage IV (LSD_F:

$P=0.001$ compared with stage I) (fig. 3A). The concentration of pNO_x^- was slightly modified by iNO in arterial (109.2 (3.1) to 119.8 (3.3) μmol litre^{-1}) and venous (116.4 (4.7) to 124.3 (4.8) μmol litre^{-1}) blood, and uNO_x^- increased from 691.2 (113.8) to 1011.3 (157.3) μmol litre^{-1} during stage II. ΔpNO_x^- increased continually during stage III compared with stage I (+22.1 and +21.4 μmol litre^{-1} in arterial and venous blood), and decreased on cessation of iNO. The value of uNO_x^- remained at the same high level during stages III and IV.

EXPERIMENTAL ARM

Infusion of phenylephrine in experiments D and E produced the same cardiovascular (table 2), renal (fig. 1B–3B) and metabolic (table 3) effects as in experiment B (W-ANOVA: $P>0.1$ on difference (II–I) between experiments B, D and E).

Both nitrergic treatments decreased LAP (−31.4% ivGTN group=experiment D; −26.3% iNO group=experiment E) and CVP (−25.7% and −19.1%, respectively), achieving the same stages-difference (III–II) between experiments D and E (LSD$_W$: $P=0.1$ for LAP and $P=0.09$ for CVP) (table 2). The effect on pulmonary hypertension was the same in both groups (table 2): PAP decreased by 13.7% and 12.4%, respectively. IvGTN decreased MAP (−39.4%) and SVR (−49.3%), and iNO induced a much smaller decrease in systemic haemodynamic variables (table 2). HR, CO and blood-gas values remained unchanged throughout the experiment.

The two nitrergic treatments did not reverse the decrease in RBFc induced by phenylephrine (fig. 1B), but they both increased UF (+148%, LSD$_F$: $P=0.0005$ for experiment D; +128%, LSD$_F$: $P=0.0004$ for experiment E) (fig. 3B). Comparison between experiments D and E on stages-difference (III–II) showed that ivGTN exerted more effect on UF than iNO (LSD$_W$: $P=0.003$). Infusion of ivGTN increased pNO_x^- concentrations compared with stage II (table 3): +22.8% for arterial blood and +26.2% for venous blood. The values in experiment E were +6.4% and +4.9% for arterial and venous blood, respectively (table 3). Both nitrergic treatments markedly increased uNO_x^- concentrations (+65.4% for experiment D and +46.3% for experiment E).

At the end of the experiment, cardiovascular, respiratory and renal (except for UF in experiments D and E (LSD$_F$: $P=0.001$ for comparison of stages IV to equivalent stages I; fig. 3B) variables essentially returned to their initial values. In experiment D, the increases in arterial and venous pNO_x^- (table 3) and uNO_x^- concentrations observed during stage III were still present during stage IV. Twenty minutes after cessation of iNO, pNO_x^- concentration significantly decreased (compared with stage III) in experiment E (table 3), whereas uNO_x^- remained high (1206.4 (108.9) μmol litre^{-1}). Comparison between experiments D and E on stages-differences (IV–III) and (IV–I) confirmed that pNO_x^- returned to baseline values in the iNO group but not in the ivGTN group.

Discussion

To our knowledge, this is the first report of PEHT in swine treated with nitrergic therapies and the first study of the haemodynamic extra-pulmonary effects of iNO.

The model used in these studies is well established. There was no mortality during the surgical preparations and we demonstrated with experiment A that cardiorespiratory variables remained stable during the period of the study and there were only minimal changes in renal function.

EXPERIMENT B

Cardiovascular effects

Phenylephrine acts on both α_1- and α_2-adrenoceptors[14] and induces hypertension (major α_1-effect) by constricting resistance and, to a lesser degree, capacitance vessels.[9] We observed no signs of tachyphylaxis with phenylephrine during the experiments. The observed passive post-capillary pulmonary hypertension with increased central filling pressures was secondary to the left ventricular haemodynamic effects of the acute increase in afterload induced by systemic hypertension. During the experiment, PVR did not change, in agreement with heterogenous[15] α-adrenergic innervation of large (5–7 mm in diameter) and small (2–3 mm in diameter) porcine pulmonary arteries and sparse or non-existant[16] α-adrenergic innervation of swine pulmonary resistance vessels.

Renal effects

The kidney reacted to phenylephrine-induced increase in SVR by a decrease in RBFc,[9] while GFR and UF remained unchanged. This suggests that phenylephrine constricted mainly the efferent arteriole and that GFR was maintained, despite a decrease in RBFc, by an increase in glomerular filtration fraction.[17]

Metabolic effects

The baseline values of pNO_x^- were higher than those measured in a porcine model of ARDS (30 μmol litre^{-1}).[7] However, the measurement techniques were different (chemiluminescence *vs* high-pressure liquid chromatography based on the Griess reaction[7]) and the surgical stress of our procedure may have stimulated release of endogenous NO. Furthermore, reported values for basal concentrations of pNO_x^- (mainly NO_3^-) in humans vary greatly.[18–20] Our basal values for uNO_x^- were in accordance with those published previously in humans.[18 20]

EXPERIMENT C

Inhaled NO alone induced no cardiorespiratory modifications, but considerably altered renal function.

Transport of EDRF–NO

Several authors have suggested that EDRF–NO interacts with circulating molecules to regulate its activity, allowing its transport (NO carriers)[21 22] or promoting its degradation (NO scavengers).[23] Metal nitrosylation with haem and non-haem proteins and the NO reaction with nucleophil groups (e.g. sulfhydryl, amine)[24] of amino acids, peptides and proteins lead to the potential interaction and formation of many nitrosyl–haem adducts, *S*-non-protein-nitrosothiols (*S*-nitroso-L-cysteine), *S*-nitrosylated proteins (*S*-nitrosoalbumins,[21] *S*-nitrosohaemoglobins[22 23]), nitrosylated iron–sulphur clusters, dinitrosyl–iron complexes,[25] nitrosoamines and others.

Renal effects

Renal haemodynamics and diuresis were altered by iNO (experiment C), strongly supporting the presence of extra-pulmonary effects. It is now widely accepted that EDRF–NO is an important modulator of RBF and that regional microcirculation[26] may be mediated by endogenously produced EDRF–NO. Pharmacological block of EDRF–NO results in an increase in MAP and renal vascular resistance, and decrements in RBF, GFR, UF and sodium excretion.[27] There is some controversy regarding a selective effect of EDRF–NO block on either afferent or efferent arteriolar tone.[26] It would seem that EDRF–NO primarily alters afferent vascular tone,[28] thereby modifying the ability of the preglomerular vasculature to autoregulate glomerular capillary pressure. Several studies have emphasized an effect of EDRF–NO not only on glomerular but also on tubular function and the medullary circulation.[28 29] McKee, Scavone and Nathanson[30] showed that EDRF–NO, through generation of cGMP and stimulation of cGMP-dependent protein kinase(s), mediates the actions of several intercellular messengers to regulate renal tubular Na–K-ATPase. Inhibition of this sodium pump (e.g. by acetylcholine, bradykinin) would decrease transcellular water and sodium reabsorption from the tubular lumen, resulting in diuresis and natriuresis. Moreover, low doses of NO synthase inhibitors, that have no effect on either RBF or GFR, induce antidiuretic and antinatriuretic effects.[31] Here is the first report of exogenous iNO modulating renal function. Renal haemodynamic state may be influenced during iNO administration by circulating NO metabolites (e.g. NO_x^-),[32] renal NO delivery through release from carrier *S*-nitroso compounds (e.g. *S*-nitrosothiols)[33] after nitrosylation in the pulmonary circulation, or a local renal effect owing to an unknown paracrine influence stimulated by iNO. *In vitro* studies have shown that $NaNO_2$ did not influence renovascular tone in concentrations up to 0.1 mmol litre^{-1}.[33] The diuretic effect of $NaNO_3$ was observed with a plasma NO_3^- concentration of 38 mmol litre^{-1} in dogs.[32] In view of the rapid renal response to application and discontinuation of iNO, we postulate that iNO may be accompanied by non-selective, extra-pulmonary effects caused by local delivery of NO on peripheral territories that include the renal bed.

Metabolic effects

Nitric oxide reaching the circulation can be metabolized via three pathways:[23] (i) interaction with dissolved oxygen in blood to form NO_2^-, (ii) reaction with oxyhaemoglobin to form methaemoglobin which in turn is reduced back to haemoglobin and NO_3^- mainly by the NADPH–methaemoglobin reductase and peroxynitrite pathways, and (iii) combination with deoxyhaemoglobin to form the stable nitrosohaemoglobin (HbNO) or with carrier molecules to form *S*-nitrosothiols among others (see above). However, to date, the mechanisms by which NO is inactivated and eliminated are not fully known.

The concentration of pNO_x^- increased almost linearly throughout inhalation, and decreased on cessation of iNO. This result is in agreement with those of previous reports[19 20] which have shown a linear temporal increase in pNO_x^-. Approximately 40 μmol of uNO_x^- were excreted in urine during the 40-min inhalation period, a result similar to that of Wennmalm and colleagues,[19] and the rate of elimination was maintained over the following 20 min. This implies that 23.6% of the retained NO was excreted in urine as uNO_x^- within 1 h after the start of inhalation. This early and fast elimination of iNO corroborates a previous study[20] that showed 69% of inhaled ^{15}NO was excreted in urine as $^{15}NO_3^-$ within 24 h and another 4% from 24 to 48 h after the start of inhalation. Moreover, the decrease in pNO_x^- and maintenance of diuresis and high uNO_x^- concentrations after cessation of iNO suggest that NO_x is stored in packaged forms before its release without vasoactive but with diuretic effects, transformation and elimination as NO_x^-.

EXPERIMENTAL ARM

Cardiovascular effects

Inhaled and i.v. nitrergic treatments partially reversed the passive pulmonary hypertension induced by phenylephrine. With the PEHT swine model, iNO 40 ppm was less effective in reducing PAP (50% reversal of the increase) than during hypoxia (108.7% at 40 ppm),[5] thromboxane-mimetic infusion (61% at 40 ppm),[6] experimental ARDS (57.1% at 40 ppm)[7] or sepsis (84% at 10 ppm;[2] 64.8% at 40 ppm[4]). PVR remained unchanged throughout the experiment suggesting that the pulmonary resistance vasculature was not constricted and that both treatments did not act at this level in the PEHT swine model. Because the pulmonary vascular tone was unchanged by nitrergic treatments superimposed on PEHT, baseline gas exchange variables also remained unchanged.

The increase in PAP induced by phenylephrine was adjusted to comparable levels in both groups. Both treatments induced similar decreases in LAP, and consequently PAP and CVP. The decrease in LAP may be explained by a decrease in left atrial filling, increase in left compliance, decrease in left ventricular afterload or a combination of these effects. The first hypothesis is unlikely because CO did not change and there was no clinical sign of an increase in lung water as gas exchange variables remained constant. The second assumption implies, from the formed cGMP,[1] block of α_1 effects on cardiac contraction and relaxation,[34] and a positive lusitropic effect increasing relaxation and diastolic distensibility of the heart.[35] A direct cardiac effect of endothelium-independent nitrovasodilators, such as depressed myocardial contractility,[36] improved ventricular relaxation and diastolic distensibility[37] is accepted. The decrease in systemic afterload (third postulate) was manifest with ivGTN infusion which induced a substantial decrease in SVR. An endogenous EDRF–NO signalling pathway has been found to regulate cardiac myocyte function.[38] The paracrine actions of EDRF–NO stimulated by substance P or bradykinin, particularly on left ventricular relaxation, are also well established.[39] The second and third hypotheses imply extrapulmonary effects with iNO. In a previous study,[5] we suggested that iNO had a direct cardiac effect. There was a slight modification of left ventricular afterload with iNO, as the observed decreases in SAP and MAP were statistically significant (LSD_F: $P=0.0001$ and $P=0.004$, respectively) (table 2). We propose that iNO had a direct cardiac effect to explain the similar action of ivGTN and iNO on PAP, LAP and CVP. Our data indicate a larger decrease in SAP and MAP than that for DAP, suggesting that factors other than aortic compliance or SVR are modified by iNO. These other factors are usually related to changes in the mechanical performance of the heart as a pump.[40] A trend for iNO to decrease SVR or MAP was observed in several publications.[2,3,7].

Renal effects

In experiments D and E, nitrergic treatments superimposed on phenylephrine infusion resulted in increases in UF without reversing the phenylephrine-induced decrease in RBFc. The primary phenylephrine site of action in the kidney seems to be the efferent arteriole in contrast with the afferent arteriole for EDRF–NO. This could explain the lack of reversibility for the decrease in RBFc induced by phenylephrine for both nitrergic treatments. Our findings also support a direct diuretic (and natriuretic?) effect of exogenous NO. Another hypothesis is the involvement of regulatory systems, either intrarenal such as the kallikrein–kinin system or prostaglandins (PGE_2), or extrarenal such as atrial natriuretic factor (ANF) or the oubain-like endogenous factor that increase diuresis.[41] However, EDRF–NO released from the endocardium or from the endothelial cells of the coronary vasculature, directly or through a decrease in LAP, or both, inhibits the release of ANF.[42] The results of experiment C and those from another study[33] give greater credence to intervention of exogenous NO in packaged forms.

Inhaled NO had a major effect on the kidney and a slight (on SAP and MAP) or no statistically apparent (on DAP and SVR) systemic effect. The kidney could be more sensitive to exogenous NO than the systemic circulation as demonstrated by the high sensitivity of RBF to NO synthase inhibition.[43] Indeed, the renovasculature showed significant modifications with low quantities of NO. Another hypothesis is that the kidney could more easily concentrate NO carriers or recuperate NO from its transport forms (local catabolism of *S*-nitroso compounds such as *S*-nitrosoglutathione, etc). The persistent diuresis after discontinuing PEHT and nitrergic treatments (stage IV) was in agreement with previous data.[32,33] It correlated with the persistent high pNO_x^- and uNO_x^- concentrations in experiment D or previous hypotheses such as intervention of other regulatory systems or a particular renal sensitivity to NO carriers for experiments C and E. It would imply that NO transported via GTN and that transported when NO is inhaled have similar (on the heart and kidney) and different (on the systemic circulation) effects. These could be explained by the nature of the implied packaged forms and their respective metabolism, particularly biotransformation of GTN to NO.

Metabolic effects

Because we deproteinized the plasma samples, NO (from iNO or released by GTN)-derived metabolites (NO_2^- and NO_3^-) and GTN-derived metabolites (1,3- and 1,2-glyceryl dinitrate, and glyceryl mononitrate) were potentially measured as pNO_x^-. At the end of stage III, infusion of ivGTN significantly increased arterial and venous pNO_x^- concentrations (table 3), and we observed only a statistical trend for iNO to increase pNO_x^- concentrations. This difference could be explained by a greater NO_x intake for ivGTN than for iNO and the larger number of metabolites of GTN. Other studies found significant differences in pNO_x^- concentrations between baseline and iNO treatment[7,19,20] with a longer period of inhalation and larger sample size.

During stage IV, pNO_x^- concentrations remained high in experiment D (ivGTN), but decreased in experiment E (iNO), whereas uNO_x^- concentrations remained high in all experiments. NO might be released during stage IV from its carrier proteins with diuretic and without vasoactive effect, and metabolized in NO_x^-. Moreover, GTN-derived metabolites could be present at the end of stage IV and measured as NO_x^-. The absence of haemodynamic effects of these compounds during stage IV could be explained by their low potency or the nitrate tolerance phenomenon. The explanation for the pNO_x^- decrease in experiment E is disruption of iNO administration.

In summary, previous studies have shown clearly a marked effect of iNO on pulmonary hypertension in pulmonary vasoconstriction models. Furthermore, in the passive PEHT model without pulmonary vasoconstriction, iNO maintained its pulmonary antihypertensive property. These results suggest that iNO may have direct cardiac effects. This study also demonstrated a marked effect of iNO on renal function, similar to that of ivGTN. We conclude that iNO had extra-pulmonary effects in an *in vivo* swine model and consequently that iNO cannot be considered as a pure selective agent on the pulmonary vasculature.

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Reduction in nitrogen dioxide concentration by soda lime preparations during simulated nitric oxide inhalation

J. WEIMANN, J. U. HAGENAH AND J. MOTSCH

Summary

Nitrogen dioxide is formed during delivery of inhaled nitric oxide for the treatment of patients with pulmonary hypertension. Soda lime has been shown to absorb nitrogen dioxide. We tested three different commercially available soda lime preparations (Sodasorb, Drägersorb 800 and Sofnolime) for their efficacy in absorbing nitrogen dioxide and nitric oxide during simulated nitric oxide inhalation. All soda lime preparations absorbed nitrogen dioxide (15%, 24% and 34%, respectively). To test if this difference could be attributed to the potassium hydroxide (KOH) content of the different preparations, two other preparations with a higher (3.0% and 7.3%w/w, respectively) KOH content were tested and we found an increase in nitrogen dioxide removal up to 47% and 46%, respectively. We conclude that soda lime absorbed nitrogen dioxide during nitric oxide inhalation. This effect seemed to be moderate under simulated clinical conditions, but increased using soda lime with a higher KOH content. Nevertheless, we recommend continuous monitoring of inspired nitrogen dioxide concentration during clinical inhalation of nitric oxide. (*Br. J. Anaesth.* 1997; **79**: 641–644).

Key words
Gases non-anaesthetic, nitrogen dioxide. Pharmacology, nitric oxide. Equipment, scavenging devices.

Inhaled nitric oxide gas is a selective pulmonary vasodilator which has been used to treat persistent primary pulmonary hypertension of the newborn,[1] primary pulmonary hypertension,[2] ARDS,[3] and pulmonary hypertension in congenital heart diseases[4] and after cardiac surgery.[5] Potential side effects of this therapy include methaemoglobinaemia and formation of toxic nitrogen dioxide.

Nitric oxide is oxidized rapidly to nitrogen dioxide in the presence of oxygen. The amount of nitrogen dioxide formed depends on the concentration of nitric oxide and oxygen in the gas mixture, and the time available for the reaction. We have demonstrated previously that the amount of nitrogen dioxide formed during nitric oxide inhalation correlated with the inspired nitric oxide concentration, the fraction of inspired oxygen and the minute volume delivered by the ventilator.[6] Nitrogen dioxide concentrations up to 2.0 parts per million (ppm) were encountered.

It has been recommended as a safety standard that nitrogen dioxide concentrations should be monitored during inhalation of nitric oxide,[7 8] but a maximum tolerable concentration of nitrogen dioxide during clinical administration of inhaled nitric oxide has not yet been defined. The Centers for Disease Control recommend an upper limit of 5 ppm of nitrogen dioxide for occupational health.[9] However, inhalation of lower nitrogen dioxide concentrations has been demonstrated to increase airway resistance,[10] reduce mucocilliary activity[11] and impair host defence[12] in humans. Animal studies showed morphological changes such as loss of cilia, hypertrophy and hyperplasia of the bronchial epithelium, thickening and fibrosis of alveolar septa, and emphysema after long-term exposure.[13–15] Studies on the pulmonary effects of nitrogen dioxide in critically ill patients are not available.

In 1967 contamination of nitrous oxide cylinders with high concentrations of nitric oxide and nitrogen dioxide led to deleterious complications during general anaesthesia[16] and prompted a study by Kain which demonstrated for the first time the ability of soda lime to absorb nitrogen dioxide.[17] Recently, a few conflicting reports have been published showing complete,[18] marked[19] or no nitrogen dioxide absorption[20] by soda lime. Some of these studies were performed by passing a constant gas flow through soda lime cylinders,[18 20] while other authors tested soda lime with delivery systems used clinically.[19]

This study was designed to investigate the efficacy of three soda lime preparations in absorbing nitrogen dioxide and nitric oxide in a clinical setting. As the major difference in the chemical composition of these soda lime preparations is the potassium hydroxide (KOH) content, we also tested the hypothesis that nitrogen dioxide absorption could be increased by increasing the KOH content of soda lime.

J. WEIMANN*, MD, J. MOTSCH, MD, Department of Anaesthesiology, Ruprecht-Karls-University, Im Neuenheimer Feld 110, D-69120 Heidelberg, Germany J. U HAGENAH, PHD, Dragerwerk AG, Moislinger Allee 53–55, D-23542 Lubeck, Germany. Accepted for publication. July 10, 1997.

*Current address for correspondence: Department of Anesthesia and Critical Care, Massachusetts General Hospital, Fruit Street, Boston, MA 02114, USA.

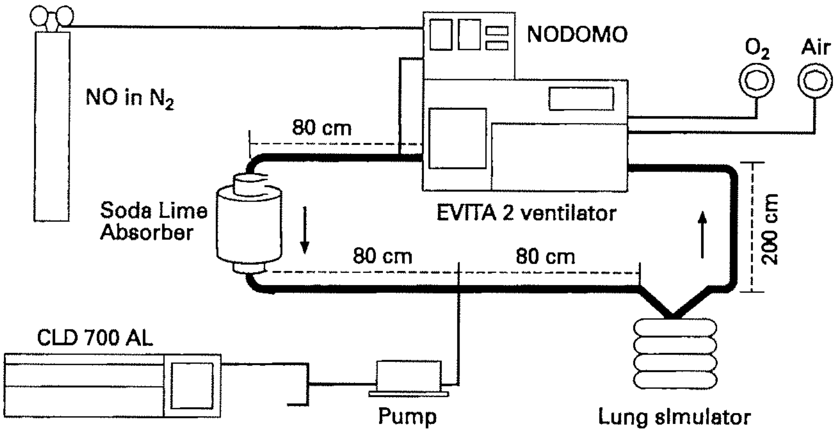

Figure 1 Scheme of the set-up, as can be used during clinical application of inhaled nitric oxide (NO). For detailed description, see text.

Methods

A mechanical lung simulator (Drägerwerk AG, Lübeck, Germany) was ventilated in a volume-controlled mode using an Evita 2 ventilator (Drägerwerk AG, Lübeck, Germany) at a constant rate of 12 bpm (fig. 1). A commercially available ventilator tubing set (polyethylene tubes with a diameter of 2.1 cm; B+P Beatmungsschläuche GmbH, Neunkirchen/Seescheid, Germany) was used in the inspiratory (length 240 cm) and expiratory (length 200 cm) limbs with a water trap in each limb connected via a Y-piece to the lung simulator.

Nitric oxide was delivered from a gas cylinder containing nitric oxide 1000 ppm in pure nitrogen (AGA, Lidingö, Sweden) into the inspiratory limb using a nitric oxide delivery device (NODOMO) (Drägerwerk AG, Lübeck, Germany). In order to maintain the nitric oxide concentration stable, the NODOMO adjusts nitric oxide flow proportionally to the flow of the ventilator.

We measured nitrogen dioxide and nitric oxide concentrations by chemiluminescence (CLD 700 AL, Zellweger-Eco-Systeme GmbH, Rösrath, Germany) in the inspiratory limb, 80 cm before the Y-connector. To prevent pressure-induced instability of the measurements caused by positive pressure ventilation, a pump was used to sample gas from the inspiratory limb. The gas sampling line of the CLD 700 AL was connected to a Y-piece at the outlet of the pump. Setting the suction rate of the pump higher than that of the CLD 700 AL ensures pressure-constant gas sampling by the CLD 700 AL. Calibration was performed after every 8 h of measurement with a gas mixture containing nitric oxide 30 ppm and nitrogen dioxide 7 ppm in pure nitrogen (AGA, Lidingö, Sweden).

An acrylic soda lime cylinder (Drägerwerk AG, Lübeck, Germany) with a diameter of 9 cm and a height of 12 cm (764 ml) was introduced into the inspiratory limb 80 cm beyond the ventilator.

To achieve different nitrogen dioxide concentrations, we changed settings for minute ventilation ($\dot{V}_E$) (5, 10 litre min^{-1}), fraction of inspired oxygen (F_{IO_2}) (0.25, 0.75, 0.99) and nitric oxide concentration (20, 40, 80 ppm). Measurements were obtained with (+SL) and without (−SL) soda lime leading to a single data pair for each setting.

Table 1 Chemical composition of the soda lime preparations tested

	Hydroxide content (% w/w)		
Soda lime	Calcium	Sodium	Potassium
Sodasorb	48.0	1.9	1.7
Dragersorb 800	45.0	2.1	2.0
Sofnolime	46.0	2.6	0.01
Special-1	44.0	3.0	3.0
Special-2	44.0	3.0	7.3

SODA LIME PREPARATIONS

We evaluated three different commercially available soda lime preparations for their ability to reduce nitrogen dioxide and nitric oxide concentrations: Sodasorb (WR Grace Co., Lexington, USA), Drägersorb 800 (Drägerwerk AG, Lübeck, Germany) and Sofnolime (Molecular Products Ltd, Thaxted, Essex, UK). Additionally, two soda lime preparations with a higher concentration of KOH were tested: Special-1 and Special-2 (Molecular Products Ltd, Thaxted, Essex, UK).

The soda lime preparations did not differ in colour indicator (ethyl violet) or granule size (4.0–8.0 mm in diameter). The chemical composition of the soda limes is given in table 1.

DATA ANALYSIS

Paired values were plotted in a scatterplot (values without soda lime (−SL) on the *X*-axis and corresponding values with soda lime (+SL) on the Y-axis). Linear regression was performed leading to the standard equation $y=mx+b$ of the fitted straight line. The difference between unity and the slope (m) of this line represents the efficiency of nitrogen dioxide or nitric oxide removal by the particular soda lime. r^2 values were calculated to test the strength of the linear correlation.

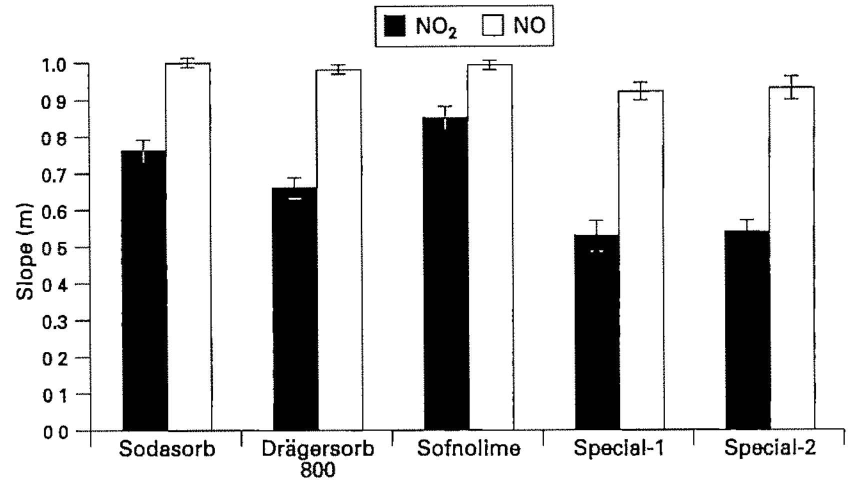

Figure 2 Reduction of nitrogen dioxide (NO_2) and nitric oxide (NO) concentrations expressed as slope values (SD of fitted lines) for the five soda lime preparations. Lower slope values indicate greater NO_2 or NO absorption.

Results

During administration of inhaled nitric oxide up to 80 ppm, nitrogen dioxide concentrations of up to 2.0 ppm were measured. The amount of nitrogen dioxide formed depended on the ventilatory setting: the higher the concentrations of inhaled nitric oxide and F_{IO_2}, and the lower the minute ventilation, the higher were the measured nitrogen dioxide concentrations.

Values of nitrogen dioxide and nitric oxide concentrations with and without soda lime showed a strong linear correlation, as indicated by r^2 values always exceeding 0.9.

All soda lime preparations reduced nitrogen dioxide concentration. Nitrogen dioxide absorption ranged from 15% (Sofnolime) to 34% (Drägersorb 800) for the commercially available soda limes and was higher for Special-1 (47%) and Special-2 (46%) (fig. 2).

While Sodasorb did not absorb nitric oxide, we found a slight reduction in nitric oxide concentration with Drägersorb 800 (2%), Sofnolime (3%), Special-1 (8%) and Special-2 (7%), respectively (fig. 2).

Discussion

We have demonstrated that three soda lime preparations (Sodasorb, Drägersorb 800 and Sofnolime) absorbed nitrogen dioxide formed during simulated ventilation with nitric oxide. Nitrogen dioxide absorption varied from 15% to 34% while nitric oxide absorption was 0–2%.

In contrast with our study, Stenqvist, Kjelltoft and Lundin[19] demonstrated a reduction in nitrogen dioxide concentrations in the inspiratory limb of their nitric oxide ventilatory system by almost 80%, but a different soda lime preparation (Q-sorb) and a larger soda lime cylinder (900 ml) were used. Ishibe and colleagues[18] showed complete absorption of nitrogen dioxide and 25% (Soda sorb) and 29% (Wako lime-A) absorption of nitric oxide using two types of soda lime. The high absorptions in the study of Ishibe and colleagues[18] may be explained by the long contact time between the gas mixtures and soda lime, resulting from a low and constant flow (1 litre min^{-1}) through the soda lime column (145 ml). Using a constant gas flow of 10 litre min^{-1}, which is more likely to represent clinical conditions, Pickett and colleagues[20] tested three different soda lime preparations. They found a marked reduction in nitrogen dioxide concentrations (80.6% and 83.9%) and a lesser reduction in nitric oxide concentrations (13.3% and 12.7%) by two types of soda lime. With a third type, both nitrogen dioxide and nitric oxide were absorbed completely as a result of an oxidizing indicator (potassium permanganate). Indicators used in commercially available soda lime preparations have no oxidizing properties. Therefore, the size of the soda lime cylinder, type (constant *vs* intermittent) and rate of gas flow through the cylinder, and chemical properties of the indicator may determine the amount of absorption of nitrogen dioxide and nitric oxide.

As the only difference between the three commercially available soda lime preparations was the concentration of potassium hydroxide (KOH), we hypothesized that the difference in nitrogen dioxide absorption may be related to the concentration of KOH. Therefore, we tested two soda lime preparations with an increased KOH content (Special-1 and Special-2). We found that nitrogen dioxide absorption increased to 47% and 46%, respectively. Nitric oxide removal was increased to a maximum of 8% (Special-2). Extending the reactions suggested by Kain[17] and Ishibe and colleagues,[18] the following chemical reactions during absorption of nitrogen dioxide and nitric oxide by soda lime may occur:

$$\begin{gathered}4NO+4NO_2+4NaOH+2Ca(OH)_2+4KOH\rightarrow\\2NaNO_2+2NaNO_3+Ca(NO_2)_2+Ca(NO_3)_2+2KNO_2+2KNO_3+4H_2O\end{gathered}$$

It is known that the radii of the hydroxides of group I elements decrease when the radius of the ion itself increases. This may account for the higher reactivity of the larger ions. As the sodium ion is smaller than the potassium ion, KOH may be more potent in binding nitric oxide or nitrogen dioxide. However, the exact mechanism by which KOH improves nitrogen dioxide absorption remains to be elucidated.

Increasing the KOH content of soda lime may be limited by the known effect of "caking", especially when humidifiers are used.[21] How the use of humidifiers may affect nitrogen dioxide and nitric oxide absorption by soda lime is not known. In one pilot experiment (unpublished data) we measured an increase in formation of nitrogen dioxide by approximately 30% when a humidifier was introduced into the inspiratory limp. Absorption of nitrogen dioxide and nitric oxide using Drägersorb 800 did not seem to be affected when measured over 10 min.

Other materials such as molecular sieve 5A[22] and charcoal[23] have been evaluated for their ability to reduce nitrogen dioxide and nitric oxide concentrations, but they lack specificity for nitrogen dioxide. While occupational exposure to nitric oxide and nitrogen dioxide in intensive care units has been shown to be low,[24 25] these and other non-selective scavengers of nitric oxide and higher nitrogen oxides were recommended to avoid environmental pollution during nitric oxide inhalation.[23 24 26]

As the dust from soda lime-containing hydroxide salts is irritating to skin and mucous membranes, appropriate handling of soda lime absorbers, as in anaesthesia systems, is essential.

We conclude that commercially available soda lime absorbed nitrogen dioxide formed during inhalation of nitric oxide. Although an increase in KOH content increased nitrogen dioxide removal, complete elimination of nitrogen dioxide from the inspired gas mixture could not be achieved. Therefore, soda lime may be helpful in preventing delivery of high nitrogen dioxide concentrations under specific clinical conditions, but continuous monitoring of inspired nitrogen dioxide concentration remains mandatory when nitric oxide inhalation is required.

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REVIEW ARTICLE

Catalogue of human error

F. ARNSTEIN

"A life spent in making mistakes is not only more honourable but more useful than a life spent doing nothing." George Bernard Shaw. *The Doctor's Dilemma*, 1913.

err. to wander, go astray, miss the mark, make a mistake, to sin.[27]

To err is human. New skills are acquired and the existing improved by practise but intrinsic to all endeavour is the prevalence of error.

For discrete work-related tasks, workers average one error in every 1000 to 10 000 acts. This apparent low prevalence is misleading because many jobs average 20 000 acts per day and some approach 100 000.[62] Examining the performance of first and second year anaesthetic trainees during simulation, De Ande and Gaba found an incidence of 6.9 unplanned incidents per case, of which 27% were considered critical.[22] Currently, most errors recognized in anaesthetic practice are discussed locally. Wider debate may be provoked by the publication of case reports and articles, and in the courts. These processes are retrospective and inherently prone to misinterpretation. This article reviews human error terminology and examines some of the factors which influence the prevalence of error. It will be suggested that all of us make errors and are susceptible to misinterpreting information. The aviation industry has long recognized this and experience gained by that industry will be outlined, suggesting methods which may be usefully adapted to anaesthetic practice. To accept error as normal is a prerequisite to establishing systems to manage the risks. To study error is to not to apportion blame but to ask why. Understanding causality enables prevention.

Errors may be classified into two major categories: active and latent.[53] Active errors are events which occur immediately before an incident or accident. Latent errors are systems containing unrecognized faults which become evident under specific circumstances.

Active errors

Active errors can be subdivided into contextual, modal or psychological.

Mistaking a 1-ml ampoule of adrenaline for atropine is a contextual error in that the mistake occurs during a particular activity. However, such a description inhibits comparison between different activities. Modal descriptions are context free and may be subdivided into errors of omission, repetition, substitution and insertion (commission), and allow easier comparisons. Such descriptors are broad so that focus may be lost and there is no attempt to describe error causation, making prevention strategies difficult to formulate. Psychological definitions aim to define cognitive mechanisms that lead to error and should make error causation predictable and comparable. Errors described in this manner have been divided into slips (action not intended) or mistakes (poor or faulty planning). Usefully, errors may be classed as knowledge, skill, or rule based, with some observers describing an additional group of technical errors.

KNOWLEDGE BASED ERRORS

Knowledge based errors originate in a background of inadequate knowledge or experience. Experience is important because it enables the deployment of a generic solution to a novel situation. However, examining the role of experience on the response to simulated critical incidents, DeAnda and Gaba suggest that experienced staff are as likely as trainees to make errors (67.5% human error compared with 72.2% and 56.6% for first and second year anaesthetic residents, respectively).[21]

RULE BASED ERRORS

Rule based errors occur when there is a failure to apply a rule or an inappropriate rule is used, for example performing cardiopulmonary resuscitation when the electrodes of the electrocardiogram have become detached. Anaesthetic seniority may confer an increased risk of making errors of this type as more short cuts are used. Such deviations are also termed violations or intentional errors.

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Key words
Anaesthesia, human error. Anaesthesia, aviation. Anaesthetist, human error.

FRANCIS ARNSTEIN, MB, CHB, FRCA, DAVMED, Department of Anaesthesia, Edinburgh Royal Infirmary NHS Trust, Lauriston Place, Edinburgh EH3 9YW.

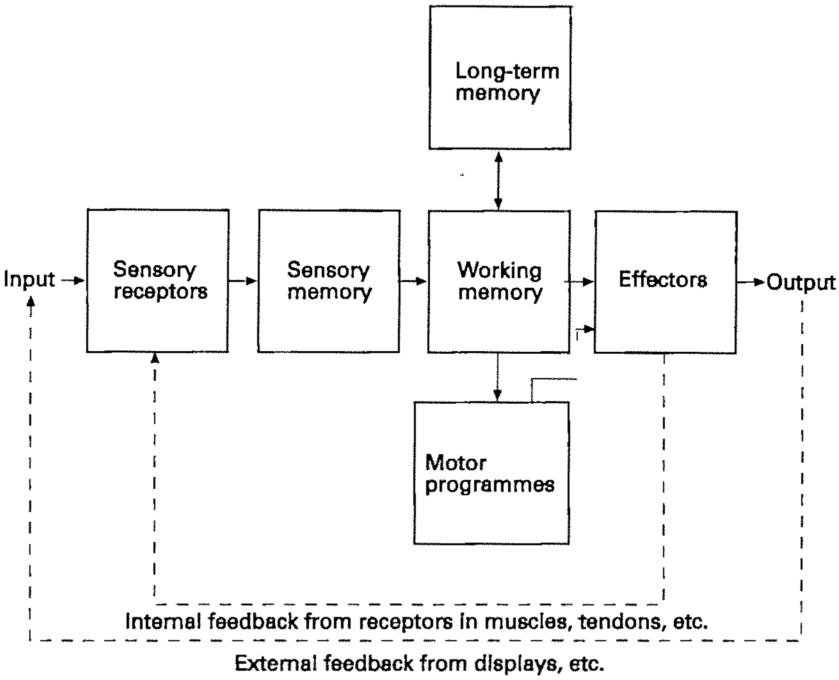
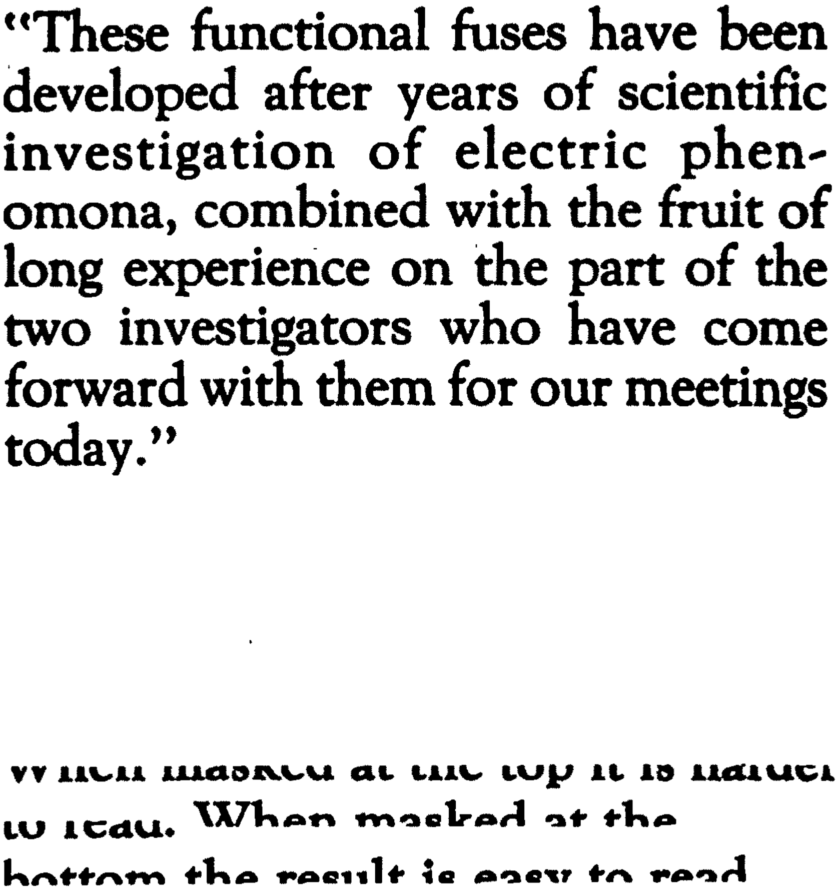


Figure 1 A model of human information processing (reproduced with kind permission of Butterworths, London).

SKILL BASED ERRORS

Skill based errors which incorporate slips and lapses relate to errors in conscious and subconscious (automatic) cognition. Human information processing may be described by the model developed by Rasmussen (fig. 1). The mind may be viewed as an information processor provided by a series of filtering sensors and memory systems enabling comprehension of a data set without conscious recognition


"These functional fuses have been developed after years of scientific investigation of electric phenomona, combined with the fruit of long experience on the part of the two investigators who have come forward with them for our meetings today."

When masked at the top it is harder to read. When masked at the bottom the result is easy to read

Figure 2 Reduncancy in writing. How many times does the letter "f" appear in the top paragraph? (reproduced with kind permission of Robson Books, London).

of the whole. For example, the written word contains much redundancy both in content and form (fig. 2).[7]

Subconscious or motor programmes enable many tasks to be performed simultaneously and rapidly, freeing cognitive power for conscious effort. Although motor programmes are fast and efficient they are also rigid and occur by definition without awareness. Therefore, it is possible (and in daily life is common) to select the wrong motor programmes for the task or develop a programme with an in-built fault. Even conscious activity requires a balance between speed and accuracy but during emergencies the time available to perform a task is often limited.

TECHNICAL ERRORS

Technical errors are described in the anaesthetic literature but originate strictly from outside the individual. For example a "failed" extradural may result from performing the procedure correctly on a patient with atypical anatomy.

Within these broad categories, sub-classifications have evolved. Norman has described five types of slip.[48]

Capture errors: fault caused by the use of an inappropriate motor programme, for example giving a neuromuscular blocking agent to a patient with a known difficult airway.

Description errors: using the correct action on the incorrect object, for example turning off the oxygen instead of the nitrous oxide. Selecting the wrong ampoule has been described as a description error or simply absentmindedness. "Absentmindedness" may be interpreted by the layman as implying carelessness and fails to recognize that such errors are intrinsically normal.

Memory errors: omitting elements of an intended action sequence.

Sequence errors: performing task elements in the wrong sequence.

Mode errors: correct action used for equipment currently in the wrong mode, for example turning off the ventilator when the breathing system is in ventilation mode.

Additionally, three further forms of error are described as *fixation errors*: despite evidence to the contrary, continuing with an inappropriate plan, dealing with everything except the real problem and believing the evidence is falsely positive.[32] These may be seen as "cognitive tunnel vision".

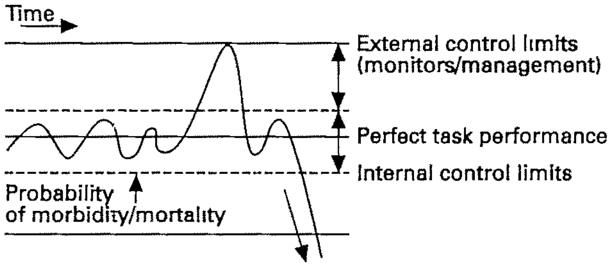

Time
External control limits (monitors/management)
Perfect task performance
Internal control limits
Probability of morbidity/mortality

Figure 3 The error train: an incident/accident model.

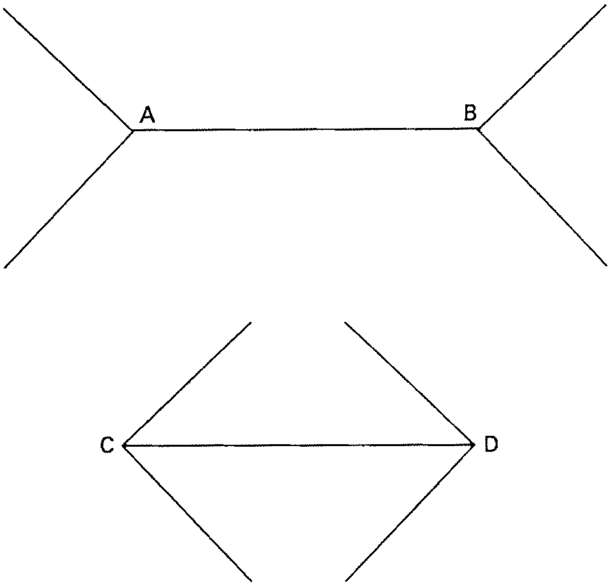


Figure 4 The power of simple illusions. The Muller–Lyer illusion. Does AB=CD? (reproduced with kind permission of Robson Books, London).

Monitoring and control systems should be in place to advise the anaesthetist that he or she is failing. These should not impinge continuously on his conscious effort. To do so may interfere with cognitive function and induce irritation. Davies described a useful incident/accident model ("Human error—prevention and investigation". Lecture given to the Royal College of Anaesthetists Anniversary Forum on *Risk Management for Anaesthetists*, 1995). This may be seen as an error train (fig. 3). Remaining on the correct and most direct track requires good internal control and when this fails, timely and accurate intervention by external monitors. Failure of both may lead to an incident or accident. The associated morbidity corresponds to the degree of deviation.

Human information processing systems may be unable to detect errors of recognition (illusions),

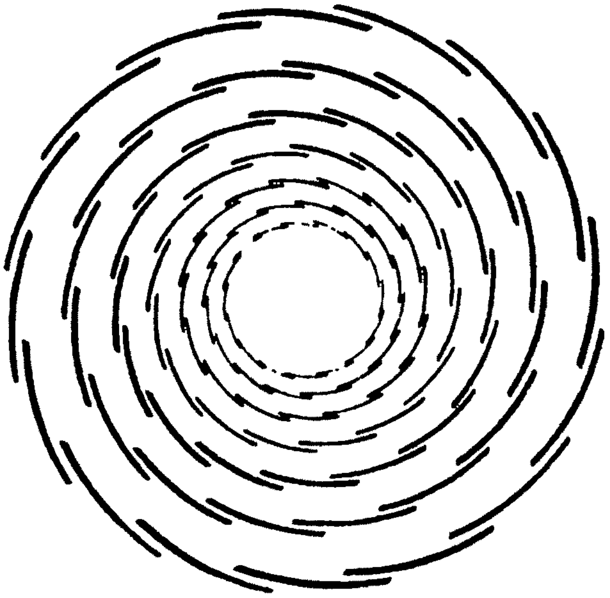


Figure 5 Fraser's spiral: spiral or concentric circles? (reproduced with kind permission of Robson Books, London)

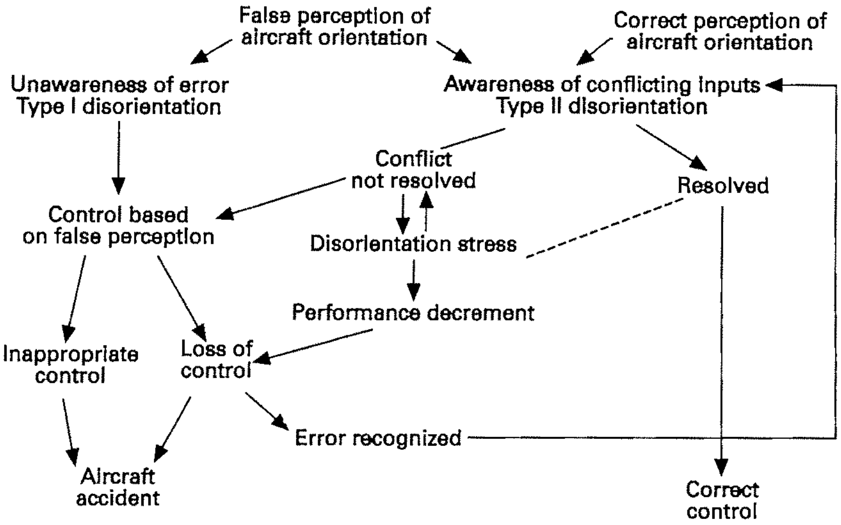

False perception of aircraft orientation
Correct perception of aircraft orientation
Unawareness of error Type I disorientation
Awareness of conflicting inputs Type II disorientation
Conflict not resolved
Resolved
Control based on false perception
Disorientation stress
Performance decrement
Inappropriate control
Loss of control
Error recognized
Aircraft accident
Correct control

Figure 6 Types I and II disorientaton in aviation (reproduced with kind permission of Butterworths, London).

imagine external stimuli (hallucinations) or may make false cognitive hypotheses (delusions). Simple illusions may be powerful (fig. 4). Prolonged exposure to one set of stimuli may affect the perception of subsequent information. Some illusions are so powerful that they are impossible to resolve leaving the observer bemused but conscious of his fallibility (fig. 5).

Failing to maintain accurate contact with reality may lead to disorientation. In aviation, two forms of disorientation incidents are recognized.[5] Type I is defined as when the pilot fails to recognize that his perception is incorrect whereas during a type II incident he senses that the cues presented to him may be inducing a false perception (fig. 6). The former represents a greater hazard in that an erroneous situation exists but the pilot remains unaware and this is supported by aviation accident mortality data. It would seem reasonable to extrapolate these modes of disorientation to other human activities, including the practice of anaesthesia.

External monitoring systems may assist in resolving the cognitive conflict but the disorientation may be so powerful that alarms are considered to be faulty and are ignored. In aviation it is recognized that it is best to avoid the circumstances which may be disorientating. Therefore, training emphasizes the early recognition of risk situations with the deployment of well rehearsed procedures to optimize the chance of maintaining accurate contact with reality. In a similar manner the use of algorithms during anaesthesia assists; 62% of anaesthetic difficulties can be resolved within 60 s by reference to basic ABCD management.[54] The use of simulation should prepare anaesthetists for rare adverse events.[33] However, it is recognized that memory deterioration demands that refresher courses should be offered at regular intervals and probably not exceeding 6–12 months.[46 60] Unfortunately, during crisis management there may not be enough time for logical analysis and printed *aide-mémoires* can be invaluable while advances in computer technology is enabling the introduction of rapid access databases.

Latent errors

Latent errors are inadequacies or failures of ergonomics or training, incorrect policies or protocols, inadequate assistance or supervision, social and cultural factors, including language, the physiological state of the patient and chance. Chance is analogous to fate, being defined as risks which have such low probabilities that estimates cannot be assigned. An example might be injury caused by metal fatigue in an operating table where such an event could not be foreseen during the design of the table or even after extensive use.

The risk associated with a latent error must be viewed with caution because to occur may require shaping or enabling factors. For example an anaesthetic monitor may cause no difficulty when used in optimal lighting conditions but the presence of screen reflections or an anaesthetist with defective colour vision[25] may degrade the information it provides so that it fails to warn and may contribute to increased stress and wasted cognitive effort.

Examples of latent errors reveal the multitude of potential problems which may act singly or in combination to induce error. Equipment may be designed by those who will not use it. The development of anaesthetic monitors has been rapid but they are rarely integrated, and they often have many alarms of similar form but representing widely differing pathophysiological states; that is cues lack specificity. Displays may be too small, use inappropriate colours and have warning messages that appear on the periphery of the screen (fig. 7). Poor integration inhibits the flow of information to the observer who must make frequent body or head movements or use saccadic vision. Audible alarms may have similar tones, and without adequate separation in loudness between alarms and background noise may be inaudible.

Inappropriate default alarm settings may prevent the monitor from warning as may failure to set the alarms. Variations in equipment and lack of training in its use increase the likelihood of error and alter the

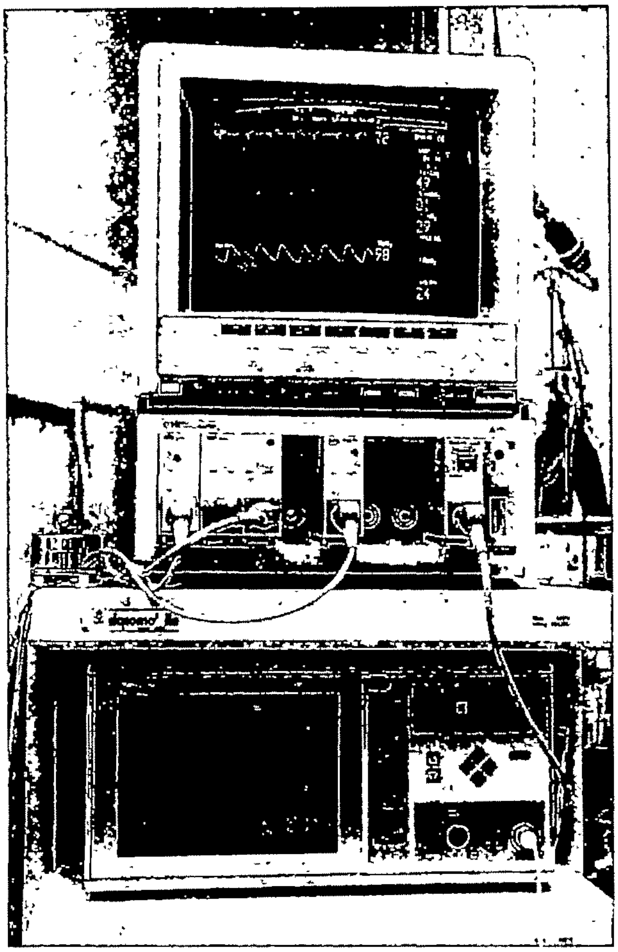


Figure 7 Ergonomic design failures in an anaesthetic monitoring system. "Alarms suspended" shown at the screen periphery (upper monitor) or shown as remainder of screen information (lower monitor)

perceived stress. Special circumstances, for example neurosurgery or MRI scanning, may prevent direct anaesthetist–patient contact, increasing dependence on monitors. An aviation analogy would be transferring from visual to instrument flight rules during poor weather or night flying, a situation recognized to increase accident rates, stress and workload.

Even simple items of anaesthetic equipment may contain the properties of a latent error, for example the packaging of disposable items such as the Guedel oropharyngeal airway using materials which may occlude the airway (fig. 8). Drug ampoule labelling has been the attention of much debate and a comprehensive solution to the misinterpretation of ampoules has yet to be found.[19 26 49 50]

Figure 8 A latent error in the packaging of a Guedel airway.

Frequently latent errors cannot be identified before an activity and only vigilance and luck prevents more incidents becoming accidents. Case reports, safety notices and the roles of the Committee of Safety in Medicines and Medicines Control Agency are examples of systems which involve vigilance but also demand dissemination of important information accurately, expediently and with clarity.

PSYCHO-PHYSIOLOGICAL STATUS

The psycho-physiological state of the anaesthetist may influence considerably the incidence of error and his or her performance. Factors to consider include the effects of immediate and underlying stress and personality trait. Eyesenck described three descriptors of personality type: extroversion (extroversion and introversion), neuroticism (stability) and psychotism. Extroversion and neuroticism have been identified as useful indicators of risk personalities in aviation and road traffic accidents but although personality tests are used by civil airlines, their use by the military is limited. Good pilots and perhaps good anaesthetists tend to be stable extroverts. Extroverts who are unstable make errors but of a different nature to introverts, tending to be risk takers enjoying the thrill of being near the edge. In contrast the unstable introvert gives in early when difficulties are mounting. In military aviation the latter may eject early with the unnecessary loss of the aircraft while the former does not eject at all with the loss of aircraft and pilot. Simple observation may identify anaesthetists who tend to fall into one category or another with associated risk taking and error prone behaviour.

Personality

The influence of personality must be viewed in the light of the presence of extraneous stressors. Although stress is usually viewed as a negative phenomenon this only describes those situations which are outside normality and necessity. In 1908 Yerkes and Dodson described a model of the

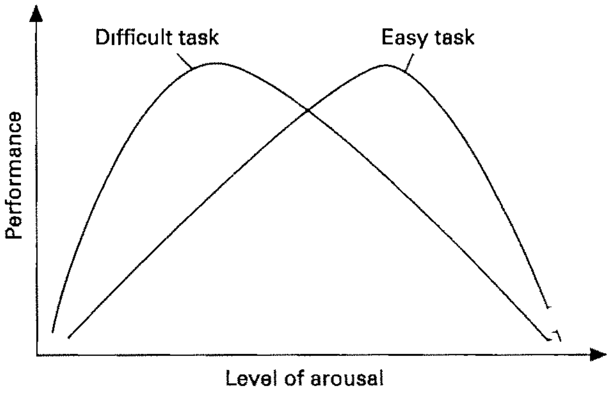


Figure 9 The Yerkes–Dodson relationship between arousal and performance (reproduced with kind permission of Butterworths, London).

influence of stressors on performance demonstrating that the optimum performance of a task occurs at a particular stress level (fig. 9).[69] Too little leads to drowsiness, reduced vigilance, errors of omission and slowed reactions. Too much results in increased response to false alarms, narrowing of attention, disruption of organized thought, startle reactions, increased speed but reduced accuracy of motor activity, and finally panic. Others support the view that excess workload results in a reduced capacity for information processing.[41] However, the Yerkes–Dodson concept can be criticized.[29] For example it suggests that an identical performance decrement will occur at high and low stress levels whereas it is recognized that these states produce opposite effects on attentional selectivity. Further, performance changes caused by heat-induced arousal are different from those caused by noise. Despite these reservations the inverted "U" relationship between arousal and performance represents a useful model.

Stress factors

Stressors appear in many forms. They may be immediate in time and place such as noise, heat, vibration and excess or too little light, or they may be more remote but no less intrusive: family and financial worries, career uncertainty, effects of unusual or excessive work schedules, poor team co-operation and the memory of prior incidents or accidents. Inadequate debriefing and support after the latter may induce a vicious cycle of increased endogenous stress and risk of accident recurrence. Stress, intrinsic to the task, may arise acutely if the task is not completed successfully. Consequently the performance of the individual may deteriorate inducing a vicious cycle of more stress and less success (synonymous with the headless chicken).

The effect of different extraneous stressors on performance has been subject to much study. Anaesthesia is often practised in noisy environments and the effects of noise have been reviewed by Kam, Kam and Thompson.[40] The perception of sound is complex and several different scales have been derived to describe sound levels, human sound perception and noise.

Aural communication between the anaesthetist and his colleagues and monitors requires an acceptable signal to noise ratio. For all the elements of speech to be heard they must be spoken at least 15 dB above the ambient noise level. However, there is much sound redundancy in speech and intelligibility depends on the content, context and prior experience of the listener. Consequently, a 10-dB separation usually allows 100% reception. Sound levels exceeding 105 dB cause discomfort, and intelligibility may fall because of sound distortion by the ear itself. Auditory alarms may be subject to auditory masking. For a second alarm to be recognized the volume required increases as the sound frequencies of the two alarms approach each other.[52]

Abrupt changes in noise level may induce startle reactions reducing performance long after the sound and is the mechanism of action of the military stun grenade. High continuous noise levels increase arousal, reducing error in repetitive, monotonous tasks. However, performance of complex tasks decreases with reduced accuracy, poor response to the unexpected, increased annoyance and induction of fatigue. Additionally the effect of noise cannot be viewed in isolation to other stressors nor can the accuracy of hearing be isolated from the performance of other faculties.

Table 1 Effects of vibration on speech, sight and motor function

Function	Organ or tissue resonant frequencies (Hz)	Effect
Speech	6–20	Loudness modulation with ↓ intelligibility
Vision	20	Intraocular structures vibrate. Facial flutter
	30–40	Vestibulo-ocular reflex: compensation with
	70	↑ effort to 25 Hz.
		Pursuit reflex: ↓ function >1 Hz or 40° s^{-1}
Motor	2–6	↓ control outstretched hands

Vibration is a stressor not commonly experienced by anaesthetists but can be of significance to those involved in patient transport, particularly in helicopters. Different structures of the human body have varying natural resonances, and exposure to vibration may impede sensory input and motor function (table 1). Helicopter flight may induce a disparity between the oscillation of the eye and the display of the monitor and intense effort may be needed in trying to obtain useful visual information. Additionally vibration may cause significant changes in arterial pressure, reduce tactile feedback, induce fatigue and motion sickness. MacNab and colleagues measured noise and vibration in emergency transport vehicles used for the transport of neonates (land, air and water) and recorded maximum vibration levels in excess of those considered extremely uncomfortable for adults.[46]

The effects of fatigue on performance and error have been assessed. Fatigue is linked to circadian influences and work schedules. Perhaps surprisingly studies have failed to show conclusively that fatigue is associated with a significant degradation in performance but some have suggested increased response times and reduced accuracy. An analysis of adverse occurrences in an intensive care unit demonstrated peak reporting between midnight and 01:00.[1] Clearly, results depend on the level of fatigue which is influenced by the time of day, time since sleep or rest, time on task and nature of task. In addition, although fatigue may not induce failure it may reduce feelings of well-being.

In 1967 Holmes and Rahe evaluated and scored life stressors in terms of life change units.[38] The development of the "schedule of recent experiences" enabled 42 life stressors to be weighted according to subjective assessments. There is a correlation between this score and the prevalence of physical and psychiatric illness. This scoring system has been criticized, particularly in its failure to separate "positive" experiences from "negative" and a further development by Sarason, Johnson and Siegel suggests that negative events are of much greater importance than change alone.[57] Life stress has been demonstrated to be present in those blamed for aviation accidents but absent from those considered blameless.[3]

Excess or adverse stress may induce failure to cope. This may result in internalization of feelings leading to social withdrawal and depression. Conversely, externalization may be suspected by increased defensiveness, hostility, arrogance, projecting blame onto others ("acting out") and risk taking. General behavioural and life style changes may develop with increased alcohol ingestion, drug misuse, fatigue and illness.

Vigilance by colleagues and managers may help identify those who are failing to cope with stress. The aviation world accepts that this is not a medical disorder in itself and has replaced the term "failing aviator syndrome" with "aviator at risk".[47] Most stress reactions are now viewed as a normal response to excess stress and are termed "adult situational reactions" with the emphasis on the transitory nature of the stressor. It is increasingly accepted that anyone could have such an experience.

A greater understanding of the effects of stress may produce an increased awareness that stress is normal, occurs in everyone's lives and is usually transitory. However, circumstances may dictate that help is needed and the systems used by the aviation industry result in a high recovery rate. To encourage discussion, it is imperative that a request for help is not construed as an admission of failure. It is important that those who assist are appropriately trained and empathetic. Education in human factors is taking a more prominent position in the aviator's curriculum and perhaps should be considered formally in anaesthetic training. There are systems for helping the "anaesthetist at risk" such as the national sick doctors scheme and at a local level the allocation of individual mentors. The publication of articles in the anaesthetic literature discussing stress in the profession demonstrates an increasing awareness and has been recognized by the Association of Anaesthetists of Great Britain and Ireland with the introduction in November 1992 of stress management courses.[24 59] These have always been over subscribed with greater interest expressed by consultants than trainees (personal communication). To admit that there is a problem is the first step to finding solutions.

I Illness?

M Medication?

S Stress?

A Alcohol?

F Fatigue?

E Eating?

Figure 10 Retaining own responsibility for current competency by checking one is not adversely affected by any of the above.

The individual can usefully retain much responsibility for assessing his or her current stress level and make a judgement as to current competency. Aviators are encouraged to use "IMSAFE" (fig.10) before each flight and this approach is readily transferable to anaesthetic practice. Reductions in trainee hours of work and increased supervision should reduce some of the elements shown.

Training and motivation may have significant effects on an individual's performance, enabling optimal results to be achieved within the constraints of personality, aptitude and cognitive resources. The Royal Air Force assesses the aptitude of potential aircrew recruits with a combination of psychometric testing (the p tests), leadership tasks and formal interviews. Specific tests such as the defence mechanism test correlate well with performance during military training and service.[37] Currently, recruitment into anaesthesia tends to be based on a short interview and the provision of written references. With the implementation of the Calman report and introduction of "career" training, more careful candidate assessment may be appropriate. The study of training and motivation forms part of the remit of psychologists working in education and industry. Clearly both have important implications on the prevalence of error.

Team effort

So far the emphasis has been on the individual and the man–machine interface. However, it is recognized that the anaesthetist represents just one part of a complex system. The Australian incident monitoring study demonstrated that the system directly contributed to 25% of problems and was implicated in 90%.[55]

Individuals may be expected to use guidelines and procedures which have been developed by others, often working as committees. The work of a committee might reasonably be expected to reach an average or measured response to a problem. However, this is not always so. "Risky shift" represents the effect of the group's solidarity in promoting a view which would otherwise be considered too extreme by any one individual. "Group think", a concept developed by Janis, is a phenomenon associated with very cohesive groups where individuals act, albeit subconsciously, to preserve the integrity of the group rather than express dissent. Consequently sensitive issues may be ignored. Importantly the committee's conclusions may be based on deliberations far removed from the situation under discussion.

Pilots work as members of a team which includes other aircrew and ground staff. Anaesthetist's work similarly requires a co-ordinated effort with other theatre staff and anaesthetic colleagues. Sharing workload within a team has advantages and disadvantages. The benefits include the allocation of task elements to individuals with specific expertise and may enable the workload for any one person to be kept to an acceptable level. However, the successful division of labour requires good leadership, communication and co-ordination. The current approach to the early management of trauma demands a well practised and cohesive specialist team. To achieve this requires time and training. Without this investment personality differences, lack of common language and intention are likely to increase the probability of error with a suboptimal outcome. In contrast with the parallel design of the trauma team, traditional management structures have tended to be of a serial format. Although the latter may emphasize the hierarchical nature of responsibility, the longer lines of communication may reduce management's awareness of the requirements of those in direct contact with patients.

Accidents may reflect the quality of senior management, a point emphasized in the official reports on the Piper Alpha explosion, the Kings Cross underground fire and Clapham Junction railway accident.[43]

The need for formal training in team management was recognized in the civil aviation industry with the introduction of line orientated flight training (LOFT) by North West Airlines in the 1970s and since then cockpit or crew resource management courses (CRM) have become an integral part of commercial civil flying training. Foushee described several examples where failure of communication within the team and poor assignment of responsibilities led to an in-flight critical incident or accident (address to the Western Psychological Association, San Francisco 28 April, 1983). Within the industry it is recognized that developments in aviation technology present new challenges to aircrews and therefore CRM training must be adapted accordingly.[14] Perhaps surprisingly the Royal Air Force does not yet recognize this need believing that the attributes are identified during the initial pilot selection process and the acquisition of additional skills is an integral part of military aircrew training.[2] LOFT involves using a high fidelity simulator to expose all the flight crew to a complete "flight" during which a simulated emergency occurs, the nature of which requires good team co-ordination to achieve a successful outcome. The simulator also enables accidents and incidents to be reproduced providing useful information during accident investigation. The development of simulators by anaesthetists should enable a similar approach to evolve but until recently most work has focused on the performance of the individual rather than the whole theatre team.[42 158] Additionally, anaesthetic simulators are considered expensive and are not commonplace. The high cost of aviation simulators is offset by the recognition that many situations cannot be safely created in the air, rare scenarios need to be practised and the high fidelity makes simulated flight essentially "real" and therefore cost effective. Ovassapian has shown that the initial acquisition of fibreoptic intubation skills using simulation can be more efficient than training with patients.[51] Commercial aviation simulators are required to be licensed and it may be that the performance of anaesthetic simulators needs to be assessed formally if simulation is to become a routine part of training. In the medico–legal field, anaesthesia is considered to be a high-risk specialty. The growth in litigation may ensure that anaesthetic simulation becomes routine and cost effective.

The performance of the team depends significantly on the qualities of its leader. In the latter half of this century psychologists have focused much of their interest on the interaction between individuals and the psychology of leadership. In 1971 Fielder proposed two orthogonal leadership factors.[30] Successful leadership requires a balance between the dual requirements of achieving the task (initiating structure) and good group relationships (consideration). Best productivity is achieved by leaders who score highly for both goal (G) and people (P) orientation. In comparison, low G and high P scores produce good quality but poor productivity and high G and low P scores result in more work achieved but of poor quality.

It is important to remind ourselves that error does not equate with negligence. However, error is often deemed culpable in retrospect. Retrospective analysis is fraught with difficulties, not least because memory degrades rapidly tending to simplicity and coherence, contemporaneous records cannot fully and accurately reproduce the actual event and investigators's interpretation may be influenced by their own prejudices. The need to examine all the circumstances surrounding an error as they existed at the time is to be emphasized. This said, Caplan and colleagues demonstrated agreement between

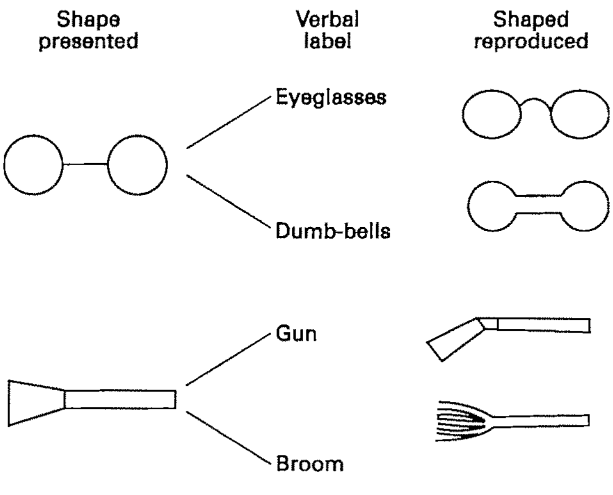


Figure 11 Effects of language on the reproduction of shapes (reproduced with kind permission of Butterworths, London).

anaesthetists of widely differing backgrounds when asked to review anaesthetic mishaps.[9] Memory may be influenced by many factors, for example auditory cues can distort visual or other memory significantly (fig. 11) and this failure is used to advantage by the legal profession.[10] Culpability may only be appropriate for situations where there was extreme departure from acceptable standard practice without any extenuating circumstances.

Identifying errors

Current systems used to identify error in anaesthetic practice are manifold (table 2). However, all have limitations, particularly in that they rarely aim to provide a complete answer to why an error occurs. Anonymous critical incident reporting has been introduced and large studies such as the Australian incident monitoring study have reached some comprehensive conclusions. In particular, it is recognized that 80% of critical incidents may have their origins in 20 categories.[65] The Royal College of Anaesthetists has published findings from its critical incident pilot study but although this categorizes the events it fails to focus on causation.[36] Focusing resources on a limited number of problems may be the most efficient method of reducing error. Critical incident reporting systems are often based on the use of questionnaires but it is recognized that these must be very carefully designed.[18 64] The use of closed questions may impose rigidity resulting in loss of valuable information whereas free expression may provide much data but no answers. The overall length and structure of the questionnaire is important if the responder is to be motivated to complete it. Careful wording of the questions is needed to minimize the problem of response sets (acquiescence: giving an answer as expected by the question; social desirability: answering as the expected norm). Semi-structured interviews have been used and may be more effective in capturing data.[16] Researchers in ergonomics have used many techniques for identifying human error: Kirwan compares 12.[42] This suggests that a universally applicable method has yet to be discovered.

Identification of an error prone situation may enable a detailed and prospective analysis of the problem to be undertaken. Several techniques have been developed which can be used to assess the workload associated with a particular flying task. The subjective workload assessment technique (SWAT) involves subjective examination of three core elements: time load, mental effort and psychological stress. These are scored by the crew at regular time intervals and then the whole task can be analysed to detect phases when workload is inappropriate and error becomes likely. Application of these techniques in anaesthetic practice may help identify periods of risk. However, such analyses are very labour intensive and the presence of an observer is likely to influence the behaviour of the observed.

The review of anaesthetic mishaps should be made by those trained in seeking the truth in a sympathetic and neutral manner. The keywords for investigators are accessibility, confidentiality and advocacy. However, occasions may demand that public safety assumes priority. Anaesthetists should be encouraged to record confidentially and anonymously their experiences as soon as possible after the event without endeavouring to analyse or justify their actions. Investigation of individual incidents should entail examination of contemporaneous records supplemented by questionnaires and interviews. The data should be pooled to provide a database from which patterns of error may emerge encouraging prevention.

The work of the anaesthetist exposes him or her to emotionally stressful situations. Involvement in cases where patients suffer unexpected injury or death can be particularly difficult to cope with, especially if the doctor considers him or herself to be at fault. Post-traumatic stress disorder (PTSD) is now a well recognized clinical disorder and was accepted into UK law after the Herald of Free Enterprise disaster. It is defined as "the development of characteristic symptoms in an individual after a psychological traumatic event that is generally outside the usual range of human experience and one that would be markedly distressing to anyone". It may last indefinitely. To minimize the development of PTSD, those involved in anaesthetic mishaps may need to undergo critical incident stress debriefing. After aviation accidents there are well established systems for helping all involved and guidelines have been published.[13]

Table 2 Current mechanisms for investigation of error, critical incidents and accidents in anaesthesia and aviation

Anaesthesia	Aviation
Discussion with colleagues	Discussion with colleagues/line manager
Discussion with senior mentor	Discussion with aviation medicine specialist
Morbidity and mortality conferences	Confidential human factors incident reporting programme
Critical incident studies/reports	Case reports and hazard notices published in journals
Medical audit	Civil Aviation Authority investigations
National mortality surveys (Scottish mortality study)	Coroner or fiscal enquiries
Employing authority enquiries	Air Accident Investigation Branch (Department of Transport)
Case reports and hazard notices published in journals	US National Transportation Safety board investigations
Coroner or fiscal enquiries	International Civil Aviation Organization reports
Confidential enquiry into peri-operative deaths	Media investigations
Medical Defence Organization reports	
General Medical Council deliberations	
Media investigations	

Table 3 Prevalence of human error in critical incidents in anaesthesia and aviation. (m)=Military aviation, (s)=anaesthetic simulation. *64% for instant reporting and 70% for retrospective analysis; †58% aircrew error/47% supervisory error, ‡hot-air ballooning

Anaesthetics (Reference)	Human error (%)	Aviation (Reference)	Human error (%)
Craig and Wilson 1981[17]	65	Sanders and Hoffman 1975 (1949) (m)[56]	62.4
Cooper and colleagues 1984[16]	64–70*	Sanders and Hoffman 1975 (1964–69)[56]	58
Kumar and colleagues 1988 (1984–86)[44]	80.3	Shuckburgh 1975 (1962–71)[61]	40–46
Currie 1989[18]	82	Sanders and Hoffman 1975 (1958–72) (m)[56]	80
De Ande and Gaba 1990 (s)[22]	65.9	Lewis 1975 (1971–73) (m)[45]	50
Wright and colleagues 1991[67]	80	Vyrnwy-Jones 1985 (1971–82) (m)[63]	75
Short and colleagues 1992 (1990–91)[60]	80	Frankenfield and Baker 1994 (1984–88)‡[31]	88
Chopra V and colleagues 1992 (1989–90)[12]	75	Yacavone 1993 (1986–90) (m)[68]	58/47†
Williamson and colleagues 1993[66]	83	Guohua Li 1994[35]	80

Prevalence of human error

To justify expending resources to reduce the incidence of human error it is important to assess the size of the problem. Mortality directly contributable to anaesthesia is quoted at 1 per 10 000 anaesthetics given to approximately 3 per 500 000.[8, 20] Morbidity is harder to estimate and is probably under reported. The risk of death in an aircraft accident is of a similar order. In 1982 there were just over 1000 fatalities in passenger aircraft accidents out of a total of approximately 755 million passengers journeys over 14 million flying hours (approximately 1 death per 75 500 passengers).[39] It is difficult to estimate the incidence of critical incidents, particularly as definitions vary. Derrington lists 10 definitions from different studies.[23] I propose the following: "a critical incident is a human error or equipment failure that if not corrected leads to an undesirable outcome. An accident is the consequence of a critical incident, which uncorrected, progressed to an undesirable outcome".

It has been suggested that the word accident represents a conceptual ambiguity and should be disqualified from technical use.[28]

Despite differences in study design and definitions, estimates of the contribution of human error to critical incidents and accidents in anaesthesia and aviation during the past 15 yr are surprisingly similar (table 3). This supports the notion that there are fundamental mechanisms causing error. The prevalence has appeared to increase in both anaesthesia and aviation which may reflect growing complexity but may also be a result of increased recognition.

Improvements in equipment, training and regulation have failed to reduce the contribution of pilot error to aviation accidents. This may reflect the increasing complexity of the aviation world. The practice of anaesthesia has also become increasingly complex. Patients and their relatives have greater expectations as do our surgical and nursing colleagues. This is reflected by the growth in medical litigation. In the USA 80% of malpractice claims filed between 1935 and 1975 were filed during the last 5 yr of that period.[11]

For commercial pilots human factors education is incorporated into cockpit or crew resource management courses and both trainees and the qualified are taught how to recognize and manage stress. Anaesthetists may benefit from similar formal training with the potential for improved team effort, staff satisfaction and patient outcome.

Conclusions

In summary, although the practice of anaesthesia is commonly deemed safe, the profession rightly seeks for continual improvement in quality. Human error remains and will probably always be the primary cause of accidents. This error may be focused on the performance of the individual, the team or the system. Its origin is likely to be multifactorial and complex to resolve. Gaba and colleagues have proposed strategies for preventing anaesthesia accidents but there is a need to continue to research into the causes of error, both in the field of research psychology and specifically in the practice of anaesthesia.[15, 34] Error and critical incident terminology needs clarification so that comparative work becomes easier. There is also a need for anaesthetists to be formally trained in human factors, including team management. Finally, the appointment of an anaesthetic accident investigation team, working independently of any medico-legal process, could provide the necessary expertise to reach valid conclusions. To this end the establishment of the Critical Incident Pilot Study Steering Group by the Quality of Practice Committee of the Royal College is a useful step.

"The greatest mistake you can make in life is to be continually fearing you will make one."

Elbert Hubbard. *The Note Book*, 1927.

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SHORT COMMUNICATIONS

Pre-emptive analgesia using local anaesthesia: a study in bilaterally symmetrical surgery

W. I. CAMPBELL AND R. W. KENDRICK

Summary

Two studies were carried out in patients undergoing bilaterally symmetrical lower third molar surgery under general anaesthesia. In the first study observations were carried out in 40 patients, using McGill pain questionnaires and visual analogue scales (VAS), to assess the variation in pain intensity between the two sides in each individual on the morning after surgery. The within-patient variation in pain intensity indicated that a sample size exceeding 30 was required to show a difference of more than 10 mm on the VAS and achieve a power of 90% at the 5% level of significance. The second study was carried out to determine if local anaesthesia administered before rather than after tooth removal rendered any benefit. Each of the 38 patients acted as their own control; one side was allocated randomly to receive the local anaesthetic before operation and the other side after operation. The difference in pain between the pretreated and post-treated sides in each individual was assessed using a McGill pain questionnaire on the morning after surgery in addition to two VAS (one for each operation side) after operation, at 6 h, 1 and 6 days after surgery. There were no significant differences in pain at any time using any of the above methods. (*Br. J. Anaesth.* 1997; **79**: 657–659).

Key words

Analgesia, pre-emptive. Anaesthetics local. Pain, measurement. Pain, postoperative. Surgery, dental.

Recent findings indicate that tissue injury may generate prolonged excitability within the central nervous system (CNS) and that postoperative pain may be reduced by preventing CNS excitation during surgery. This hypothesis is based on animal work which showed that elimination of spinal cord bombardment by nociceptive transmissions prevented cord hyper-excitability.[1] Preliminary clinical research appeared to substantiate the advantage of pre-emptive analgesia,[2] but other studies were unable to confirm that there was any benefit from preoperative administration of analgesia compared with postoperative administration.[3]

Most studies in acute pain illustrate large inter-patient variation in the rating of pain intensity. Many factors such as sex, age, race, anxiety and pain tolerance may alter the level of perceived pain.[4 5] In an attempt to reduce these confounding variables to a minimum, this study was designed so that patients would act as their own control. The aims of the study were to quantify the difference in pain intensity between two sides of the body when bilaterally identical surgery was carried out and thus determine a sample size for further studies of this type, and to determine if preoperative administration of local anaesthetic rendered any advantages compared with postoperative administration.

Methods and results

This two part study was granted approval by the Ethics Committee of the Queen's University of Belfast. We studied 40 ASA I and II patients undergoing removal of both lower third molar teeth, provided that the teeth were bilaterally symmetrical on radiological examination. If upper third molars were also to be removed, patients were included only if all four third molars were removed. Informed verbal consent was obtained in each case. Before surgery, patients were shown how to complete a pain questionnaire, which they retained and completed on the morning after surgery, before returning it to the authors. Pain assessment was carried out using twin 10-cm vertical visual analogue scales (VAS), one for each operation side. Anchor points were 0=no pain, 100=worst pain possible. A long form McGill pain questionnaire was also completed on the morning after surgery. Patients were requested to complete the VAS on the left of the page for left-sided pain and the VAS on the right side of the page for right-sided pain. Then they completed a single McGill pain questionnaire by placing the letters L (left), R (right) or R+L (both sides) beside the words which described the sensation which they experienced on the day after surgery.

The procedure was carried out under general anaesthesia. Anaesthesia was induced with propofol and maintained with 1.5% halothane and 60% nitrous oxide in oxygen during spontaneous

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W. I. CAMPBELL, MD, FFARCSI (Department of Anaesthetics); R. W. KENDRICK, MB, FDSRCPS, FFDRCSI (Department of Oral Surgery); The Ulster Hospital, Dundonald, UNDAH Trust, Belfast BT16 0RH. Accepted for publication: June 19, 1997.

Correspondence to W. I. C.

breathing via a nasal tracheal tube. Surgery was commenced on the right side in the first 20 consecutive patients and on the left side in the subsequent 20 consecutive patients. The same surgeon operated on both sides, and if more difficulty was experienced on one side that patient was excluded. Surgical difficulty was rated by the surgeon after operation as: I=simple elevation; II=bone removal or tooth division; III=bone removal and tooth division; IV=very difficult. Postoperative analgesia comprised co-codamol (codeine 8 mg and paracetamol 500 mg), two tablets 4-hourly, as required.

Another 40 ASA I and II patients were studied and written informed consent was obtained in each case. These patients were given a pain questionnaire and instructed on its use after surgery, as described earlier. This pain questionnaire had two VAS to be completed 6 h after surgery, on the morning after surgery and 6 days after operation. A McGill pain questionnaire was included with the VAS to assess pain on the morning after surgery. All pain assessments were to be completed, as during the first part of the study, and posted back to the authors.

General anaesthesia was carried out as in the first part of the study, except that perioperative local anaesthesia was also used. Restricted randomization was carried out using shuffled, sealed envelopes to allocate patients to one of two groups. Group A received an inferior alveolar and a long buccal nerve block, using 0.5% plain bupivacaine 2 ml at each site, on the left side only. If the upper third molars were also to be removed, buccal infiltration with 0.5% plain bupivacaine 1 ml was administered on the left side. Surgery then commenced on the right (contralateral) side and when this was complete local anaesthetic was injected as above on this side. Those patients allocated to group B were treated in an identical manner to those in group A but the sides treated with local anaesthetic before or after surgery were reversed.

The purpose of the above procedure was to establish two groups, each of 20 patients, one with surgery commencing on the right and the other with surgery starting on the left side. Regardless of the grouping, the first side operated on was always the side which was blocked by local anaesthetic after exodontia. Surgery did not start on the second side until at least 10 min had elapsed after pretreatment with bupivacaine. A gradual decline in heart rate on completion of surgery on the first side, and lack of sympathetic response on starting surgery on the second side helped confirm adequate local anaesthetic block before surgery started on the second side.

Both the anaesthetist and patient were blinded as to the side which was pretreated. If surgery was more difficult on one side or patients were not bilaterally numb and pain free, they were excluded from the study and their randomization envelope reallocated to the next available patient who met the entry criteria for the study.

The Wilcoxon matched pairs signed rank test was used to compare individual differences in VAS and McGill pain questionnaire scores. The Mann–Whitney *U* test was used to test for differences in pain associated with the first side operated on, dominant hand and difficulty of surgery. The 5% level of significance was used throughout.

Thirty women and 10 men were observed in the first part of the study: mean age was 23 (range 18–32) yr and mean weight 65 (SD 11.9) kg. The number of patients within each difficulty of surgery grading (I, II, III and IV) was two, 13, 22 and three, respectively. There was no relationship between pain intensity and difficulty of surgery, or between pain intensity and the first side operated on. In four cases, the dominant hand was the left, and the first side operated on was the dominant side in 18 cases. Pain scores were not dependent on the dominant side. There was no significant difference in pain intensity, as assessed at 24 h with either VAS or McGill pain questionnaires (table 1). From these results it was determined that at least 30 subjects would be required if a similar study design was used to evaluate analgesia, to achieve a difference of 10 mm and 90% power at the 5% level of significance.

Thirty-one women and nine men took part in the second part of the study but two women were excluded from group A; one because of unilateral excessive bleeding and the other because of unilateral infection after operation. Mean age was 23 (range 18–41) yr and mean weight was 65 (SD 9.7)

Table 1 McGill pain questionnaire and visual analogue scale pain ratings for the first and second side operated on in patients undergoing bilaterally symmetrical lower third molar extraction under general anaesthesia alone ($n=40$). Medians (interquartiles) are also given for the difference in pain rating between the two sides in each individual (second minus first side scores.) There was no significant difference between the two sides, using either form of pain assessment, on the morning after surgery

	Median (interquartiles)
Pain assessment on the morning after surgery	
Visual analogue scale	
First side	18 (7.3, 36.8)
Second side	18 (13.3, 39.8)
McGill pain questionnaire	
First side	9 (4.3, 15)
Second side	10 (6.3, 15)
Difference in pain assessments between sides on the morning after surgery (second minus first side)	
Visual analogue scale	1.0 (−1.5, 7.8)
McGill pain questionnaire	0 (0, 1.0)

Table 2 Difference in pain ratings between the first and second side operated on in patients ($n=38$) undergoing bilaterally symmetrical lower third molar extraction under general anaesthesia. In each case, patients received local anaesthetic after tooth extraction on the first side and local anaesthetic 10 min before tooth extraction on the second side. There was no significant difference in pain between the two sides at any time after surgery

Differences in measured pain intensity (second minus first side)	Median (interquartiles)
Visual analogue scale differences at	
6 h	0 (−8.8, 5.3)
1 day	0.5 (−8.3, 5.0)
6 days	0 (−2.0, 2.5)
McGill pain questionnaire differences at	
1 day	0 (−1.0, 0.3)

kg. The number of patients within each difficulty of surgery grading (rated I–IV) was six, 19, 9 and four, respectively. Pain intensity did not correlate with difficulty of surgery or the first side operated on. All data were therefore pooled and the difference in pain between the first and second sides operated on in each patient used to establish if there was an overall meaningful difference in pain intensity (table 2). There was no significant difference in pain at any time between the two sides.

Comment

Animal research over the past few decades has demonstrated the benefits of analgesic treatment before rather than after noxious stimulation.[1] Recent clinical work has not confirmed these potential benefits[3] and it is uncertain whether or not pre-emptive analgesia occurs as a clinically useful entity. It may well be that local anaesthesia only postpones the time at which central sensitization takes place.[6]

Our initial study was established to determine the validity of using each patient as their own control. Although similar bilateral studies have been carried out in the clinical situation in the past, patients were not acting as their own controls at the same moment.[7 8] This study was designed to do this but general anaesthesia was required to assess the efficacy of local anaesthesia. Our technique is limited in that only "single shot" treatments can be tested, as subsequent treatments affect both sides, reducing the response difference. Bilateral symmetrical surgery could, however, be carried out under local anaesthesia to study the pre-emptive effectiveness of i.v. analgesics, for example non-steroidal anti-inflammatory drugs, if administered after commencing surgery on the first side.

Although the initial study may have minimized variables such as age, sex, race, anxiety and personality, there was still sufficient within-patient variation to require a minimum of 30 subjects. This symmetrical study design probably did not eliminate small differences in surgery and hence tissue damage, despite the procedure being carried out by the same surgeon. We therefore studied well in excess of 30 subjects to ensure sufficient study power.

Although pre-emptive local anaesthesia did not appear to have advantages over postoperative use, it rendered these patients pain free during the first few hours after surgery, when pain would be at its most intense.

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British Journal of Anaesthesia 1997; 79: 660–661

Intra-articular morphine and clonidine produce comparable analgesia but the combination is not more effective

M. GENTILI, P. HOUSSEL, M. OSMAN, D. HENEL, A. JUHEL AND F. BONNET

Summary

Both intra-articular morphine and clonidine produce analgesia. This study was designed to compare the analgesic effects of the two drugs, used separately and in combination. We studied 90 patients undergoing arthroscopy of the knee under general anaesthesia. Patients were allocated randomly to receive 20 ml of intra-articular isotonic saline solution containing morphine 2 mg, clonidine 150 μg or both. Pain was assessed on an visual analogue scale after operation and time for rescue medication was measured. There was no difference in VAS scores between the three groups and the time for rescue analgesic was comparable. We conclude that intra-articular morphine and clonidine have comparable analgesic effects in the doses used. The combination of both drugs did not seem to increase analgesia. (*Br. J. Anaesth.* 1997; **79**: 660–661).

Key words
Analgesia, postoperative. Analgesics opioid, morphine. Sympathetic nervous system, clonidine. Analgesic techniques, regional, i.a.

Since the first clinical studies which demonstrated that intra-articular administration of morphine could provide analgesia, related to a peripheral mechanism of action,[1] this technique has become popular and is used commonly to provide analgesia after arthroscopic knee surgery. Morphine has also been combined with bupivacaine to augment analgesia.[2] More recently, clonidine has been shown to provide analgesia when administered into the knee joint after arthroscopy.[3] As subcutaneous administration of clonidine was not effective in producing analgesia, a local mechanism of action was hypothesized.[3] Morphine and clonidine have synergistic analgesic effects when given intrathecally but not i.v.,[4] but the effect of the combination is not known when administered intra-articularly. Therefore, this double-blind, prospective, randomized study was conducted to compare the analgesic effects of morphine and clonidine when used alone and in combination.

Methods and results

After obtaining informed consent and Ethics Committee approval, we studied 90 ASA I–II patients undergoing knee arthroscopy. Surgery was performed under general anaesthesia using propofol 2 mg kg^{-1} and alfentanil 10 μg kg^{-1} for induction, and isoflurane and 50% nitrous oxide in oxygen for maintenance. Patients were allocated randomly in one of three groups according to the analgesic regimen. All received 20 ml of intra-articular isotonic saline solution before tourniquet release containing morphine 2 mg (group M), clonidine 150 μg (group C) or both (group M+C). Pain was assessed after operation using a visual analogue scale (VAS) at 1, 2, 3, 6 and 24 h after intra-articular injection. Patients received propacetamol 2 g i.v. when they complained of pain (VAS >4). Patients were also monitored for arterial pressure, heart rate and sedation, and side effects (nausea, vomiting or pruritus) were also noted.

Data were analysed using the Mann–Whitney *U* test for patient data. Median and ranks of VAS scores were compared using Kruskall–Wallis analysis. The number of patients not given propacetamol was compared using the Kaplan–Meyer method and a log-rank test.

The three groups were comparable in age (group C, 36 (range 19–69) yr; group M, 36 (18–72) yr; group M+C, 36 (20–70) yr), weight (group C, 73 (SD 10) kg; group M, 72 (10) kg; group M+C, 67 (11) kg) and height (group C, 173 (8) cm; group M, 172 (8) cm; group M+C, 171 (9) cm). Group C included 20 men and 10 women, group M, 23 men and seven women and group M+C 19 men and 11 women (ns). Mean durations of surgery were 37 (18) min, 35 (20) min and 30 (13) min in groups C, M and M+C, respectively. VAS scores were comparable in the three groups (fig. 1) but the scores decreased significantly over time. Seventeen patients in the morphine and clonidine groups and 16 in the morphine–clonidine combination group did not receive propacetamol (ns). The number of patients who did not require additional analgesia in the post-operative period was comparable in the three groups. Arterial pressure and heart rate did not change

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M. GENTILI, MD, P. HOUSSEL, MD, D. HENEL, MD, A. JUHEL, MD, Clinique Saint Vincent, 35000 Rennes, France. M. OSMAN, MD, F. BONNET*, MD, Service d'Anesthésie-Réanimation, Hôpital Tenon, Paris, France. Accepted for publication: June 2, 1997.

*Address for correspondence: Service d'Anesthésie-Réanimation, Hôpital Tenon, 4 rue de la chine, 75020 Paris France.

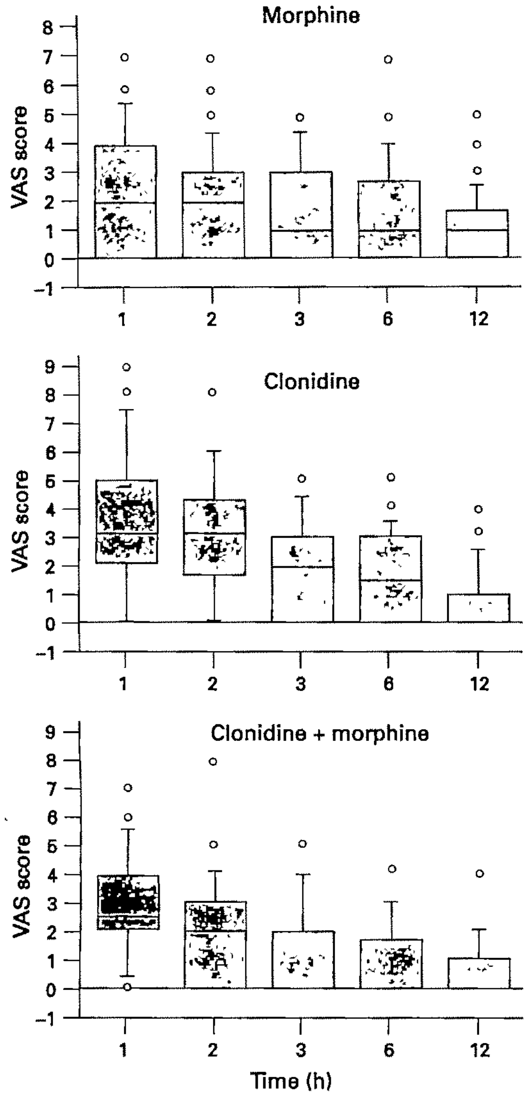

Figure 1 Pain after arthroscopy in the morphine, clonidine and clonide–morphine combination groups (mean, 10th and 90th percentiles). Boxes=25th and 75th percentiles; O=Data outside the 10–90th percentile interval.

significantly. No patient complained of sedation or other side effects.

Comment

We have found that intra-articular morphine 2 mg was equivalent to clonidine 150 μg in terms of post-operative analgesia. In all groups, mean VAS scores were low and rescue medication was limited. The hypothesis that a more painful surgical procedure could have elicited a difference between the two study drugs nevertheless cannot be excluded. For this type of procedure (knee arthroscopy) both drugs appeared to provide effective analgesia in the majority of patients although some patients may have experienced a more painful postoperative course despite intra-articular injection.

We did not compare morphine and clonidine with placebo; this comparison has been performed in previous studies and both drugs were demonstrated to be superior to placebo.[1 3] A local analgesic action of morphine is thought to be mediated by axonal endogenous opioid receptors[5] while inhibition of noradrenaline release could explain the analgesic action of intra-articular clonidine.[3] The lack of side effects commonly noticed after i.v., extradural or parenteral administration of drugs confirms that a local action probably accounts for most of the analgesic effect.

When combined, the two drugs were not more effective than each given separately. One possible explanation for the lack of additive effect is that morphine and clonidine induced complete pain relief during the first hours after operation and that no additional effect was required or measurable. Nevertheless, 50% of patients received pro-pacetamol at some time during the study, implying that analgesia could be potentially improved. We conclude that small doses of morphine or clonidine provided comparable analgesia after intra-articular administration, but that the combination of these doses of the two drugs would not be useful.

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British Journal of Anaesthesia 1997; 79: 662–664

Autotransfusion in major orthopaedic surgery: experience with 1785 patients

B. Borghi, E. Pignotti, M. Montebugnoli, A. Bassi, M. Corbascio, N. de Simone, K. Elmar, U. Righi, A. M. Laguardia, S. Bugamelli, F. Cataldi, R. Ranocchi, M. A. Feoli, T. Bombardini, G. Gargioni, A. G. Franchini and G. C. Caroli

Summary

Using a prospective audit, we have evaluated the efficacy of an integrated autotransfusion regimen which comprised predepositing and intra- and postoperative blood salvage in major orthopaedic surgery. We examined prospectively the records of 1785 patients (1198 females, 5867 males, mean age 62 (range 16–90) yr, preoperative haemoglobin concentration 13.4 (SD 1.4) g dl^{-1}) undergoing total hip arthroplasty (THA, 1229 patients), THA after removal of internal fixation devices (RFD+THA, 18 patients), total knee arthroplasty (TKA, 263 patients), revision surgery of the hip (HR cup+stem revision, 197 patients; cup revision, 53 patients; stem revision, 16 patients) and total knee revision (TKR, nine patients). We estimated that the number of predonations (MSBOS=maximum surgery blood order schedule) was 2 u. for THA, TKA and TKR, and 3 u. for partial or total hip revision and total hip arthroplasty with fixation removal. We found that it was possible to obtain the MSBOS in 1597 patients (89.5%). Homologous red blood cell (HRBC) transfusions were carried out in 131 patients (7.3%). We found that the need to use HRBC was significantly associated with failure to meet the number of MSBOS, female sex, lower preoperative haemoglobin concentration, use of calcium heparin for antithrombosis prophylaxis, more extensive surgery, higher ASA rating and co-existing diseases such as coronary artery disease. (*Br. J. Anaesth.* 1997; **79**: 662–664).

Key words
Blood, transfusion. Transfusion, autotransfusion. Blood, salvage. Anaesthesia, audit. Surgery, orthopaedic.

Autologous blood transfusions are used widely to decrease the risk of homologous blood transfusion. The techniques used in autotransfusion for major orthopaedic surgery include predonation of blood, haemodilution and intra- and postoperative recovery of red cells for re-transfusion.[1 2]

This prospective audit was designed to examine the success rate of a regimen devised in our institution for autotransfusion in major orthopaedic surgery based on predonation of blood and intra- and postoperative recovery. Our policy dictates that 2 u. of predonated blood should be obtained for total hip arthroplasty, total knee arthroplasty and total knee revision, and 3 u. are required for partial or total hip revision and for total hip arthroplasty with fixation removal. We termed these requirements the maximum surgery blood order on schedule (MSBOS). During predonation and the first week after surgery, iron is administered i.v. During surgery, uncoagulated blood is collected into a reservoir using an aspirator and collection bag connected to the inferior edge of the surgical wound. If there is a decrease in haemoglobin concentration of more than 2 g dl^{-1} (or even lower when the risk of homologous transfusion is very high, for example patients with anaemia, coronary heart disease or low body weight),[2] a kit is attached to the reservoir to concentrate, wash and reinfuse red cells (Compact-A Dideco, Mirandola MO, Italy). In the postoperative period, bleeding is monitored using the BT797 recovery Dideco and if postoperative blood loss exceeds 200 ml for the first 8 h after sedimentation and microfiltration, red cells are reinfused. The predonated blood is reinfused over the first 3 days after surgery in order to compensate for the decrease in haemoglobin concentration which normally occurs in this period.[2]

Homologous red concentrated red cells (HRBC) are transfused only when correcting hypovolaemia, when autologous blood has been reinfused, when symptomatic anaemia is present (vertigo, dizziness, postural hypotension, headache, insomnia, confusion, tachycardia, angina, dyspnoea) or when haemoglobin concentration decreases to less than 6 g dl^{-1} (10 g dl^{-1} in patients affected by cerebrovascular or coronary artery disease).

Methods and results

We studied 1785 consecutive patients (1198 females and 578 males) in three departments of the Rizzoli

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B. Borghi*, MD, M. Montebugnoli, MD, M. Corbascio, MD, N. de Simone, MD, K. Elmar, MD, U. Righi, MD, A. M. Laguardia, MD, S. Bugamelli, MD, F. Cataldi, MD, R. Ranocchi, MD, M. A. Feoli, MD, T. Bombardini, MD, G. Gargioni, MD, A. G. Franchini, MD, G. C. Caroli, MD (1st Service of Anaesthesia and Intensive Care); E. Pignotti (Statistical Analysis); A. Bassi, MD (Transfusion Centre); IRCCS, Rizzoli Orthopaedic Institute, Bologna, Italy. Accepted for publication: July 8, 1997.

*Address for correspondence: 1° Servizio Anestesia, Istituti Ortopedici Rizzoli, Via Pupilli 1, 40136 Bologna, Italy.

Orthopaedic Institute, Bologna, Italy. Mean age of the patients was 62 (range 16–90) yr and mean preoperative haemoglobin concentration was 13.4 (SD 1.4; range 6.7–18) g dl^{-1}. The types of surgery comprised total hip arthroplasty (THA, 1229 patients) THA after removal of internal fixation devices (RFD+THA, 18), total knee arthroplasty (TKA, 263 patients), total hip revision (cup+stem THR, 197 patients), cup revision (cup R, 53 patients), stem revision (stem R, 16 patients) and total knee revision (TKR, nine patients).

General anaesthesia was administered to 1182 patients and extradural with general anaesthesia to 595 patients. Eight patients received spinal anaesthesia. A total of 119 patients were classified as ASA I, 1144 as ASA II, 486 as ASA III and 36 as ASA IV. In this study 1384 (77.5%) patients had co-existing disease; 809 (45.3%) had a body mass index of 28–33 kg m^{-2}; 23 (1.3%) were obese (BMI >33 kg m^{-2}); 423 (23.7%) had systemic hypotension; 249 (13.9%) chronic obstructive airways disease; 216 (12.1%) coronary artery disease (CHD); 98 (5.5%) diabetes; 75 (4.32%) cardiac arrhythmias; 67 (3.7%) previous deep vein thrombosis or pulmonary thromboembolism; 62 (3.5%) liver disease; 43 (2.4%) rheumatoid arthritis; 33 (1.8%) cardiac valvular disease; 32 (1.8%) renal disease; 9 (1%) transient ischaemic attacks; and 25 (1.4%) anaemia (haemoglobin concentration <10 g dl^{-1}). There was no co-existing disease in 401 (22.5%) patients. For antithrombotic prophylaxis, calcium heparin (Ca He) was given to 267 patients, low molecular weight heparin (LMWH) to 230 patients and indobufen (antiplatelet agents) to 1286 patients. Two patients suffered from coagulation disorders and did not receive therapy.

Data were analysed statistically using SPSS 6.1 for Windows with contingency tables with Fisher's exact test (CT), contingency tables with Pearson chi-square test (CPT), and one-way analysis of variance with Levene test for uniformity of variances (ANOVA).

It was possible to obtain the required number of predonations (MSBOS) in 1957 patients (89.5%). In the other 188 patients (10.5%), the preoperative haemoglobin value did not allow us to achieve the target number of predonations. Mean basal haemoglobin concentration was significantly lower in the no MSBOS group (12.6 (SD 12.5) g dl^{-1} *vs* MSBOS 13.5 (1.4) g dl^{-1}) (ANOVA <0.001)). A total of 131 (7.3%) patients received homologous red blood cell transfusions (HRBC). The need for HRBC was influenced by the following: number of predonations (MSBOS 5% (80 of 1517) of patients compared with no MSBOS (27.1%; 51 of 137 patients) (CT, P=0.0001)); sex (females 8.6% *vs* males 4.8%) (CT, P<0.0049)); low baseline haemoglobin concentration (12.3 (SD 1.6) *vs* 13.5 (1.3) g dl^{-1}) (ANOVA, P<0.0001)) (fig. 1); age (67.8 (9.9) *vs* 62.1 (11.3) yr) (ANOVA, P<0.0001)); higher ASA status (IV 18.7% *vs* III 10.1% *vs* II 6.6% *vs* I 0%) (CPT, P=0.0001)); and co-existing disease (CHD 15.7 *vs* no CHD 6.2%) (CT, P<0.0001)). Thirty-two (0.7%) patients were transfused with HRBC because of haemorrhage or haematoma.

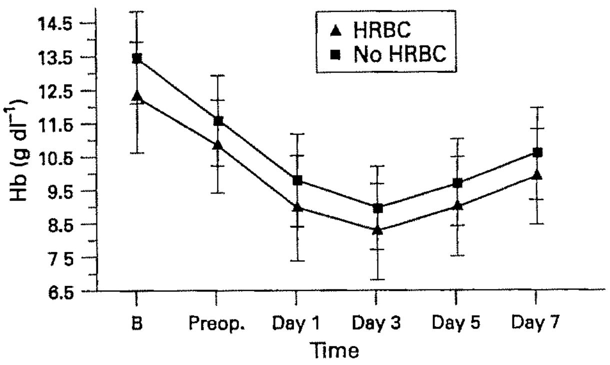

Figure 1 Perioperative changes in haemoglobin (Hb) concentration in patients treated with homologous red blood cells (HRBC) or without (No HRBC) (mean, SD). B=Baseline.

The numbers of patients treated with intraoperative salvage and postoperative salvage are shown in table 1. Administration of HRBC correlated with the type of surgery (THR 16.2% *vs* cup R 11.3% *vs* RPS+THA 11.1% *vs* stem R 6.2% *vs* THA 6.1% *vs* TKA 5.7% *vs* TKR 0%) (CTP, P=0.0001)), ASA group (ASA IV 18.7% *vs* III 10.1% *vs* II 6.6% *vs* THA 6.1% *vs* TKA 5.7% *vs* TKR 0%) (CTP, P=0.0001)), type of antithrombotic prophylaxis (Ca He 18% *vs* LMWH 7.8% *vs* indobufen 5%) but was not influenced by the type of anaesthetic, duration of surgery, amount of intra- and postoperative recovery of blood, extent of postoperative blood loss or interval between the last donation and surgery.

In 85 patients without cerebrovascular disease or ischaemic heart disease and a haemoglobin concentration greater than 11 g dl^{-1}, some of the predonated blood was not reinfused. Patients who underwent HRBC had significantly lower perioperative haemoglobin values (ANOVA, P=0.0001) (fig. 1).

Table 1 Number (%) of patients studied, and number treated with intraoperative salvage (IOBS), postoperative salvage (POBS) and homologous red blood cells (HRBC). Mean (SD) IOBS, POBS and postoperative blood loss (POBL)

	Patients (*n*)	IOBS (*n*)	POBS (*n*)	HRBC (*n*)	IOBS (ml)	POBS (ml)	POBL (ml)
THA	1229 (68.8%)	1085(88%)	1196 (97.3%)	75 (6.1%)	256 (153)	385 (239)	648 (308)
TKA	263 (14.7%)	56 (21.3%)	257 (97.7%)	15 (5.7%)	162 (92)	576 (308)	920 (399)
THR (cup+stem)	197 (11%)	197 (100%)	195 (98.9%)	32 (16.2%)	526 (361)	438 (288)	753 (371)
Cup R	53 (2%)	53 (100%)	53 (100%)	6 (11.3%)	421 (296)	354 (224)	554 (257)
Stem R	16 (1%)	15 (93.7%)	16 (100%)	1 (6.2%)	298 (174)	420 (237)	649 (364)
RFD+THA	18 (1%)	18 (100%)	18 (100%)	2 (11.1%)	769 (873)	583 (282)	997 (411)
TKR	9 (0.5%)	5 (55.5%)	9 (100%)	0	204 (133)	343 (175)	799 (449)
Total	1785 (100%)	1429 (80%)	1744 (97.7%)	131 (7.3%)	290 (241)	421 (237)	703 (348)

Comment

The Compact-A Dideco apparatus used in our institution causes less damage to red cells than cells predonated in SAG-M and kept in the refrigerator for 21 days at 4 °C,[3] and enables a higher concentration of 2,3 diphosphoglycerate and higher physiological concentration of potassium than the donor's blood[4] and explains the absence of any correlation between the amount of intra- and postoperative blood loss and use of HRBC. Other workers have reported the use of autologous blood alone in 28–62% of cases for this type of surgery by only carrying out predepositing.[5 6] With the use of only intraoperative blood salvage, it has been reported that in 28–90% of cases, autologous blood alone was used.[7 8] Where predisposition, intraoperative salvage and postoperative salvage were used in combination, autologous blood was used exclusively in 83–93.7% of cases.[1 2 9] When patients have low preoperative haemoglobin concentrations, it may be possible to use human erythropoietin to increase the amount of blood which may be obtained in advance of surgery in order to decrease the extent of homologous red cell transfusion.[10]

We conclude from this prospective evaluation of our policy for autotransfusion that red cell predisposition and intra- and postoperative salvage in combination is an effective technique for avoiding the use of homologous red cell transfusion.

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British Journal of Anaesthesia 1997; 79: 665–667

Continuous intra-arterial blood-gas monitoring in infants and children with cyanotic heart disease

M. HATHERILL, S. M. TIBBY, A. DURWARD, V. RAJAH AND I. A. MURDOCH

Summary

We have evaluated the accuracy and reliability of the Paratrend 7 continuous blood-gas analyser in infants and small children under conditions of severe hypoxaemia admitted to the paediatric intensive care unit in the perioperative period with cyanotic congenital heart disease. P_{O_2}, P_{CO_2} and pH (hydrogen ion concentration) were measured continuously via a femoral arterial sensor and compared with 100 simultaneous paired arterial blood-gas measurements. Data were analysed by Bland–Altman analysis for bias and precision. Sensors were placed in 10 children of median age 5.43 (range 0.03–45) months, median weight 3.74 (2.79–15.4) kg and remained in place for up to 27 h after operation. P_{O_2} values were 2.5–8.2 kPa (median 5.3 kPa). Co-oximeter saturation ranged from 37.1% to 90.6% (median 75.8%). Bias and precision values were 0.04/0.87 kPa for P_{O_2}, −0.44/0.74 kPa for P_{CO_2} and −2.61/6.98 nmol litre^{-1} for hydrogen ion concentration (i.e. 0.02/0.06 for pH). We conclude that perioperative continuous arterial gas monitoring is clinically accurate under conditions of severe hypoxaemia in small infants and children with cyanotic congenital heart disease. (*Br. J. Anaesth.* 1997; **79**: 665–667).

Key words
Hypoxaemia. Heart, congenital defects. Infants. Children. Monitoring, blood gases. Equipment, gas analysers.

Continuous intra-arterial blood-gas monitoring has been available in adult anaesthesia and intensive care for several years, although routine use is limited to a few centres.[1 2] The clinical use and accuracy of the Paratrend 7 system (Biomedical Sensors, High Wycombe, UK) has been established previously in humans and recent reports have documented the experience of continuous blood-gas analysis in children.[2 3]

In paediatric practice, application of this technology is likely to have maximum impact in paediatric intensive care units and operating theatres. Children undergoing cardiac surgery are one group likely to benefit from continuous monitoring, especially in the perioperative and immediate postoperative periods. However, there is a paucity of data on the accuracy of such systems under the condition of severe hypoxaemia, commonly present in children with cyanotic congenital heart disease. As previous studies have excluded smaller children and infants, there is also a lack of data on the safety and reliability of these devices in these patients.[3–5]

We present our experience of perioperative continuous intra-arterial blood-gas monitoring using the Paratrend 7 system in small infants and children with cyanotic heart disease.

Methods and results

The study was approved by the Hospital Ethics Committee. We studied children admitted to the paediatric intensive care unit (PICU) with severe hypoxaemia caused by cyanotic congenital heart disease. Only patients in whom continuous blood-gas monitoring was indicated for clinical reasons were recruited. These included infants admitted for correction of congenital cardiac defects in whom the sensor was sited before operation and children admitted after cardiac surgery and cardiopulmonary bypass in whom it was sited in the immediate postoperative period. Because of the small size of the patients, the sensor was left *in situ* for the first day after operation only, as a precautionary measure.

The Paratrend 7 sensor is a heparin-bonded element which consists of a modified Clarke electrode measuring P_{O_2}, a fibreoptic system and chemical indicator complex for measurement of P_{CO_2} and pH (hydrogen ion concentration), and a thermocouple for measurement of temperature. Oxygen saturation and base deficit are calculated. *In vitro* 90% response times for changes in pH, P_{CO_2} and P_{O_2} are reported to be 78, 143 and 70 s, respectively.[2] The sensor itself is less than 0.5 mm in diameter and is advanced within a closed-system connection via a 20-gauge cannula into the femoral artery.

Arterial pressure is transduced via a Y-connection to the device through which arterial blood is sampled in the usual manner. During the study the arterial pressure waveform was monitored for evidence of

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M. HATHERILL, MRCP, S. M. TIBBY, MRCP, A. DURWARD, FCP, V. RAJAH, MRCP, I. A. MURDOCH, MRCP, Paediatric Intensive Care Unit, 9th floor, Guy's Hospital, St Thomas' Street, London SE1 9RT. Accepted for publication: July 15, 1997.
Correspondence to M. H.

Table 1 Data for children monitored by continuous intra-arterial blood-gas analyser

Patient No.	Diagnosis/procedure	Age (months)	Weight (kg)
1	Hypoplastic left heart (HLHS)	0.03	2.7
2	HLHS/ Norwood Stage 1	0.1	2.9
3	HLHS/ Norwood Stage 1	0.03	3.2
4	HLHS/ Norwood Stage 1	0.03	3.7
5	Fallot's repair	9.6	3.7
6	Transposition of great arteries	1.2	3.7
7	Glenn shunt	15.7	8.6
8	Glenn shunt	17.8	9
9	Glenn shunt	29.8	9.6
10	Glenn shunt	45	15.4

cannula malfunction and the limb assessed continuously for evidence of ischaemia.

We studied 10 infants and children, median age 5.43 (interquartile range (IQ) 0.05–17.09; range 0.03–45) months, median weight 3.74 (IQ 3.33–8.92; range 2.79–15.4) kg (table 1).

Ten paired blood-gas measurements were made per patient, using the read-out from the Paratrend and a simultaneous arterial blood-gas (ABG) sample analysed at patient temperature (1420 Blood Gas Analyser, Instrumentation Laboratories, Birchwood, UK). The coefficients of variation for the bench ABG analyser are given as 2.1%, 6.4% and 13% for P_{O_2}, P_{CO_2} and pH, respectively. Hydrogen ion concentration was calculated from the measured pH values for the purpose of statistical analysis. Oxygen saturation calculated by the Paratrend was compared with paired measurements obtained by co-oximetry (682 Co-oximeter, Instrumentation Laboratories) and pulse oximetry (M1020A/66S Pulse oximeter, Hewlett Packard, Berkshire, UK).

The manufacturers provide a facility to correct the Paratrend read-out for "perceived bias" if readings are consistently different from simultaneous ABG values after prolonged use. This facility has been used in previous studies evaluating the bias and precision of the system, but was not used in this study.[2]

Bias and precision were calculated as the mean difference between the paired measurements, and the limits of agreement (2 SD) of these differences. Data were analysed graphically by Bland–Altman analysis, and by linear regression for historical comparison.[6]

One hundred paired measurements were performed up to 27 h after insertion of the sensor. Oxygen saturation measured by co-oximetry ranged from 37% to 90% (median 75.8%; IQ 66.7–82.6%). P_{O_2} measured by the ABG analyser was 2.5–8.2 (median 5.3; IQ 4.3–6.2) kPa. P_{CO_2} was 2.71–7.09 (median 4.76; IQ 4.44–5.19) kPa. pH was 7.14–7.59 (median 7.39; IQ 7.37–7.44).

Bias and precision values for P_{O_2} were 0.04/0.87 kPa (r^2=0.64) (fig. 1). Variation in ABG/Paratrend P_{O_2} difference did not increase with duration of insertion of the sensor or at extremes of haemoglobin concentration. Bias and precision values were −0.44 /0.74 kPa (r^2=0.76) for P_{CO_2} and −2.61/6.98 nmol litre^{-1} (r^2=0.89) for hydrogen ion concentration (i.e. 0.02/0.06 for pH).

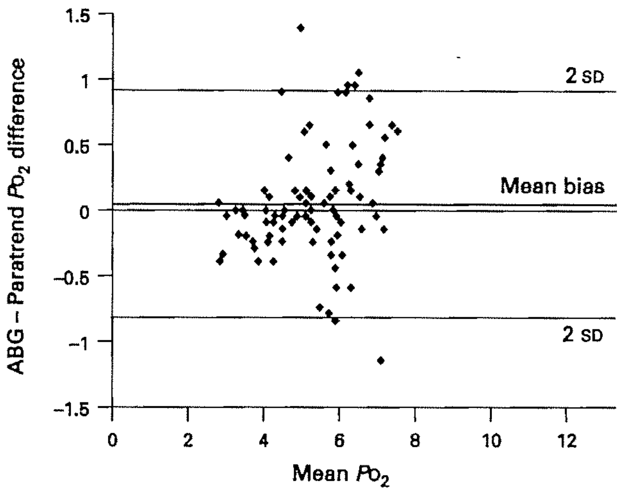

Figure 1 Bland–Altman anaysis of bias and precision for P_{O_2} (kPa) measured by the ABG and Paratrend (mean (±2 SD)).

Bias and precision values for oxygen saturation calculated by the Paratrend and measured by co-oximetry were 2.4/9.5% compared with 0.2/4.3% for oxygen saturation measured by pulse oximetry and co-oximetry.

Sensor malfunction, presumably caused by kinking as a result of patient handling, resulted in removal of the sensor in two children after 11.5 and 18.5 h, respectively. One patient with hypoplastic left heart syndrome in whom the sensor was placed before operation later developed necrotizing enterocolitis and died after stage 1 Norwood operation.

Comment

The ability to monitor continuous changes in arterial blood-gas variables is of particular interest to anaesthetists and intensivists involved in the management of children before, during and after complex cardiac surgery. Many of these patients undergo surgery for correction of cyanotic heart disease during the first year of life, underlining the importance of a continuous intra-arterial system which is accurate and reliable both in small infants and under conditions of severe hypoxaemia.

The benefits of an indwelling continuous sensor in the perioperative period include the ability to respond promptly to acute cardiovascular or ventilatory changes, minimization of blood loss in small infants and reduction of the risk of infection.

Previous studies have evaluated the clinical accuracy of the Paratrend sensor in adults and older children.[1–5] However, several of these studies included methodological errors related to correction of "perceived bias" during the study period and the use of large numbers of measurements in a single patient.[2 3] We performed 10 paired measurements in each patient and did not adjust measurements to correct for perceived bias during the study, although this may be indicated after prolonged insertion (beyond 24 h) in the clinical setting.

The bias and precision (limits of agreement or 2 SD) of the sensor demonstrated clinically acceptable accuracy for measurement of pH (H$^+$), P_{CO_2}

and $P\mathrm{O}_2$ under conditions of severe hypoxaemia ($P\mathrm{O}_2$ <8 kPa). The limits of agreement for $P\mathrm{O}_2$ in this study were 0.87 kPa, which compares favourably with the results of previous studies (single SD) which ranged from 0.91 to 3.4 kPa. Our results did not reflect the higher variability of $P\mathrm{O}_2$ measurements compared with $P\mathrm{CO}_2$ and pH reported by other workers. Previous authors have reported a single SD ranging from 0.53 to 0.81 kPa for $P\mathrm{CO}_2$ and from 0.024 to 0.06 for pH.[1–5] Although our study included only the first post-operative day, there did not appear to be any decay in the precision of $P\mathrm{O}_2$ measurement with time. Further studies of cyanotic infants, including larger patient numbers and longer insertion times, are necessary to confirm this finding. There was no deterioration in accuracy for $P\mathrm{O}_2$ measurement at either high or low extremes of haemoglobin concentration. The bias and precision of oxygen saturation calculated by the continuous analyser compared favourably with that of previously published work in cyanotic patients.[7,8] However, we were surprised to find that calculated oxygen saturation appeared less accurate than that measured by pulse oximetry in this group.

Our study population was both younger and smaller (<10 kg) than those previously reported. There were few problems with femoral artery access or introduction of the sensor, even in patients weighing less than 5 kg. The sensor failure rate (two of 10) was acceptable considering the learning phase involved in the introduction of a new technique, and can be minimized by careful patient handling.

We conclude that continuous indwelling blood-gas analysis using the Paratrend system is practical, reliable and clinically accurate in infants with cyanotic heart disease.

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CASE REPORTS

Extradural catheter-related infections in patients with infected cutaneous wounds

M. Bengtsson, H. Nettelblad and F. Sjoberg

Summary

We report three previously healthy individuals, aged 19–40 yr, with co-existing infected lower limb cutaneous wounds, who developed, in all probability, spinal space infections complicating continuous extradural analgesia. As the number of patients with extradural catheters and large cutaneous wounds represents a small fraction of the total number of patients with extradural catheters, three cases of presumed spinal space infection over a 4-yr period suggests that extradural analgesia with a catheter technique in this clinical situation is unsafe.

Key words
Anaesthetic techniques, extradural. Infection, spinal. Equipment, catheters extradural.

In a recent article by Jakobsen, Christensen and Carlsson,[1] it was concluded that extradural analgesia with a catheter technique is "a relatively safe procedure" in the surgical treatment of abscesses or infected wounds. Our experience is different. Between 1991 to 1995 we encountered three trauma patients with large open cutaneous wounds who developed, in all probability, spinal space infections after extradural catheter analgesia. Taking into account the small referral area (approximately 1 million inhabitants), the risk of developing an extradural infection may be higher than anticipated previously. A summary of the data from these three cases is given in table 1. (*Br. J. Anaesth.* 1997; 79: 668–670).

Case reports

CASE NO. 1

A 20-yr old, previously healthy farmer sustained a traumatic amputation of his right leg at thigh level combined with major blood loss. After initial resuscitation at a nearby hospital an extradural catheter was inserted at the L3–4 interspace on the second day. At this time the large cutaneous wound in the thigh showed clinical signs of infection and he had an increased white blood cell count of 18.0×10^9 litre^{-1} and a temperature of almost 39 °C. Cefuroxime and clindamycin were commenced. In the skin area above the right hip another cutaneous wound, 3×7 cm, was found. At the time of the second wound revision, the second day after the trauma, the extradural catheter was changed and a new extradural catheter was inserted at the T12–L1 level. Bupivacaine 0.25% and adrenaline 1:200 000 with the addition of sufentanil were delivered via the catheter at a constant infusion rate. There were signs of an ongoing coagulopathy as platelets decreased to 100×10^9 litre^{-1}, activated partial thromboplastin time increased to 45 s (normal range 23–34 s) and prothrombin complex decreased spontaneously to 40% (normal range 70–180%). The wounds were revised a third time. As the status of the patient did not improve, he was transferred to the Department of Plastic Surgery, Linkoping University Hospital on the sixth day after injury. On arrival the patient had a temperature of 40 °C with pain at the site at which the second extradural catheter had been inserted and a stiff neck. The puncture site was found to be red. Antibiotic therapy was changed to cefotaxime. Computer tomography (CT) scan (without contrast medium) was normal, apart from gas bubbles in the spinal canal, but lumbar puncture and analysis of cerebrospinal fluid showed an increased lactate concentration of 4.6 mmol litre^{-1} (reference value <2.1 mmol litre^{-1}). However, direct microscopy of cerebrospinal fluid did not reveal any bacteria or fungi but showed a significant amount of white cells. Simultaneous cultures from the tip of the extradural catheter, the large cutaneous hip wound and urinary tract yielded significant growth of *Pseudomonas aeruginosa*. After removal of the extradural catheter the patient's status improved significantly and by the next day he had a normal temperature. Signs of meningism disappeared simultaneously.

CASE NO. 2

The right foot of a previously healthy 40-yr-old man was crushed in a log-splitter. He was treated initially at a local hospital. Twelve days after injury he was referred to the University Hospital for skin coverage

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Mats Bengtsson, md, phd (Department of Anaesthesiology); Hans Nettelblad, md, phd (Department of Hand and Plastic Surgery); Folke Sjoberg, md, phd (Department of Anaesthesiology and Department of Hand and Plastic Surgery); University Hospital, S-581 85 Linkoping, Sweden. Accepted for publication: July 17, 1997.

Correspondence to N. B.

Table 1 Clinical and bacteriological summary. NI=Not investigated

Patient No.	Duration of catheterization	Presumed infection	Organism isolated from		Sequelae
			Catheter tip	Skin wound	
1	6 days	Meningitis	*P. aeruginosa*	*P. aeruginosa*	None
2	3 days	Abscess	NI	NI	Back pain
3	16 days	Abscess	*S. aureus*	*S. aureus*	None

of the open wound at the site of the partially amputated fore foot. As he was developing phantom pains, an extradural catheter was inserted at the L3–4 interspace and continuous infusion of 0.25% bupivacaine given. Two days later a leak was observed around the catheter. At the same time the patient complained of pain radiating from the region in which the catheter was inserted through the skin. The pain increased the following day. At this point a major wound revision was performed and a split thickness skin graft was applied to the fore foot. The following day dicloxacillin was given as his temperature had increased to 39 °C and the pain from the back area had increased, radiating to the right thigh. The patient also complained of intense headache. The puncture site around the extradural catheter was red and slightly swollen. Suspecting an extradural infection, we changed from dicloxacillin to cefuroxime treatment and removed the extradural catheter. Analysis of cerebrospinal fluid showed a white cell count of 124×10^6 litre^{-1} (normal value 0–5×10^6 litre^{-1}). Unfortunately cultures were not taken at this point. As the patient's body temperature increased further, the next day magnetic resonance tomography (MRT) with contrast medium was performed. MRT (T1-weighted images) showed a process starting from the subcutaneous area extending intraspinally between the spinous processes of L3 and L4, measuring $15 \times 30 \times 25$ mm and dislocating the dura in the right portion of the spinal canal. There was no contrast enhancement in the central part of the process, indicating pus. The neurosurgeon recommended conservative treatment. The status of the patient improved slowly over the following 3 or 4 days. However, during the postoperative period the patient complained of radiating pain in his lower back, still a complaint 2 yr after the injury.

CASE NO. 3

A few days after arthroscopy of her left knee a 19-yr-old woman developed significant iatrogenic lymphoedema. Four months after operation she developed painful opioid-resistant infected ulcers on her left foot requiring vancomycin treatment. Seven months after arthroscopy, a tunnulated extradural catheter was inserted at the L3–4 interspace through which 0.25% bupivacaine and morphine were given. Eleven days after insertion of the catheter the patient had a pyrexia (39.7 °C). On day 14 after catheter insertion the patient had increasing pain radiating out from the back. A culture from the tip of the now withdrawn extradural catheter revealed *Staphylococcus aureus*, the same strain that had been cultured from the ulcer on the foot. A CT scan (using contrast medium) showed increased contrast accumulation at the L3–4 intraspinal level extending to the intervertebral holes at the L3–4 level on the right side and a large abscess in the psoas musculature at the L2–5 level. In relation to the paravertebral musculature of the spinal process of the L3 vertebra, cone-shaped contrast enhancement of the extradural catheter track was seen. The next day, under x-ray guidance, this abscess was punctured transcutaneously and drained. Low back pain and septic fever decreased rapidly. The increased white blood cell count and C-reactive protein concentration normalized within 1 week. Unfortunately, the pain problem (in the foot) and the open ulcers continued for another year leading eventually to amputation.

Discussion

We believe that these three cases demonstrate the potentially higher risk of a serious infectious complication after extradural catheter analgesia in patients with infected wounds, in comparison with what has been stated previously[1] or been found in a general intensive care unit population with the well known risk of nosocomial infections.[2] As bacterial cultures showed growth of the same bacterial strains from both the infected wounds and the catheter tips, the likelihood of haematogenous spread between the two sites as a cause of the infectious complication must be regarded as high. None of the cases had open wounds in the immediate vicinity of the puncture site of the extradural catheter, and the catheter was tunnelled in one case. The extradural catheters were inserted by three different anaesthetists, making substandard aseptic technique an unlikely culprit. For these reasons haematogenous spread seems more likely and direct contamination at the puncture site less likely to have been the process responsible. None of the patients was known to have reduced immunocompetence, diabetes mellitus or any other concomitant disease.

Among several reasons for the low incidence of spinal space infections after extradural catheterization one might be antimicrobial activity of the local anaesthetics used. The bactericidal effect is concentration-related and has been shown to be most marked with 0.5% bupivacaine, and less with lower concentrations.[3] Of interest is a study by James and colleagues[4] showing that 0.25% bupivacaine was 5–25 times as potent at 37 °C compared with at room temperature in decreasing the colony count of different bacterial isolates. All of our patients received bupivacaine in a concentration of 0.25% or slightly less (because of dilution by addition of opioid). The extradural solutions were made up by a ward nurse under aseptic conditions using 50-ml syringes that were used immediately and changed in less than 12 h.

The medical management strategy pursued in case No. 2 has been described previously.[5]

The incidence of this type of infectious complication is difficult to evaluate from our material. Whether the previous retrospective investigation of 120 extradurals[1] is to be regarded as too small to determine the true rate of a rare complication is debatable. Our intention is to highlight the fact that these infections do occur and should prompt a high degree of clinical suspicion in any physician responsible for the care of patients with painful open wounds and an extradural catheter. These three cases have also prompted us to restrict the practice of using extradurals in this type of patient.

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A case of cardiac hydatidosis

S. LAGLERA, M. A. GARCIA-ENGUITA, F. MARTINEZ-GUTIERREZ, J. P. ORTEGA, A. GUTIERREZ-RODRIGUEZ AND A. URIETA

Summary

We present the case of a female patient with a diagnosis of hydatidosis located in the heart. Although echinococcosis is endemic to our country, very few cases of cardiac hydatidosis are normally reported. In our patient, the hydatid cyst was located in the septum and in the right ventricular cavity; it presented other unusual features, such as the fact that it was located exclusively in the heart, that it first manifested as anaphylactic shock of unknown origin and that it required immediate surgical treatment because of severe haemodynamic compromise. (*Br. J. Anaesth.* 1997; **79**: 671–673).

Key words

Complications, echinococcosis. Complications, hydatidosis. Infection, parasitic.

Echinococcosis is a disease produced by the encysted larvae of echinococcal worms. There are four species pathogenic to human: *E. granulosus*, *E. multilocularis*, *E. oligarthrus* and *E. vogeli*. The most frequent is *E. granulosus* which is endemic in areas of the Mediterranean coast, Middle East, Australia, New Zealand and South America,[1] although it is spreading to other non-endemic countries as a result of immigration.

Echinococcus multilocularis, the causative agent of human alveolar echinococcosis, is found usually in countries of the Northern Hemisphere. *E. oligarthrus* and *E. vogeli* are endemic to Central and South America.

It is agreed that cardiac involvement of echinococcosis occurs in approximately 0.5–2% of all cases, although these values are taken from a study performed in 1958, and are therefore debatable.[2–4] The occurrence of severe complications, such as sudden death and cyst rupture, in cardiac cavities or in the pericardium makes cyst extirpation the most appropriate treatment.

This report describes a case of cardiac hydatidosis and discusses its clinical manifestations, diagnosis, treatment and anaesthetic implications.

Case report

A 49-yr-old female patient with a history of tonsillectomy and brucellosis was admitted suffering anaphylactic shock which had manifested without previous trauma or strain. After treatment at home with adrenaline, dexchlorpheniramine and prednisolone s.c., she was transferred to hospital.

On examination the patient showed signs of low cardiac output and ventricular tachycardia, which was controlled with lignocaine i.v. An ECG performed after remission of symptoms showed ST-segment elevation in leads V1–V3. Chest radiography revealed a small overgrowth of the left ventricular cavity.

Three days after admission, the patient presented with instability, cyanosis, hypotension and a body temperature of 38 °C. The EEG showed subepicardial ischaemia on the anterolateral wall. Echocardiography demonstrated a cystic mass in the interventricular septum with right ventricular cavity collapse. A thoracic computed axial tomography (CAT) scan confirmed the existence of a cystic mass as described by echocardiography and excluded any lung involvement. Abdominal CAT excluded the presence of other cystic masses.

With a diagnosis of cardiac hydatidosis and haemodynamic decompensation, the patient was transferred to a hospital with cardiac surgical facilities. On admission, she was stabilized haemodynamically and she exhibited moderate dyspnoea. Prednisolone 1 g i.v., dexchlorpheniramine 5 mg i.v., ranitidine 50 mg i.v. and midazolam 1.5 mg i.v. were administered 1 h before surgery.

During surgery, we monitored ECG, invasive arterial pressure, central venous pressure and peripheral oxygen saturation. Anaesthesia was induced with midazolam 2 mg, fentanyl 0.2 mg, etomidate 16 mg and vecuronium 6 mg. High-dose vecuronium and fentanyl were given by continuous infusion to maintain anaesthesia, and the lungs were ventilated with 100% oxygen. Surgery was performed under extracorporeal circulation with a 45-min perfusion time and an ischaemia time of 25 min.

The incision exposed an intramyocardial hydatid cyst, 10×7.5 cm, located on the right ventricular

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S. LAGLERA*, PHD, M A. GARCIA-ENGUITA, MD, J. P. ORTEGA, MD, A. URIETA, PHD (Department of Anaesthesiology and Reanimation); F. MARTINEZ-GUTIERREZ, MD, A. GUTIERREZ-RODRIGUEZ, MD (Department of Cardiac Surgery); Miguel Servet Hospital, C/ Isabel La Católica s/n, Zaragoza, Spain. Accepted for publication: July 8, 1997

*Address for correspondence: C/ Rubén Darío 6, Zaragoza 50012, Spain.

wall and apical septum with leftwards displacement of the anterior interventricular artery. The cyst had ruptured at the apex of the right ventricular chamber with an orifice of 1 cm in diameter. The surgical field was isolated with a protective layer soaked in hypertonic saline solution 20% which was used as a scolicidal agent. On discontinuing cardiopulmonary bypass, the patient required inotropic support (dopamine $5\ \mu g\ kg^{-1}\ min^{-1}$).

The only postoperative complication was paroxysmal supraventricular tachycardia, detected 7 h after surgery. It caused no haemodynamic problems and was treated with amiodarone i.v. ECG revealed complete block of the left branch of His bundle. As soon as oral feeding was restarted, albendazole 400 µg/12 h for 28 days was given. The patient was discharged 9 days after surgery.

Discussion

Echinococcus enters the heart via the coronary circulation, either via a permeable foramen ovale or the pulmonary circulation.[5,6] The embryo reaches full growth at 1–5 yr after being lodged in the heart. The myocardial reaction to the cyst creates an adventitial pericyst layer.[3,5,6]

Although any part of the heart may be affected, the most common location of the cardiac hydatid cyst is the free wall of the left ventricle (50–77%) or the interventricular septal wall. Damage to the pericardium occurs in 50% of cases. Most patients (55–85%) also manifest multivisceral failure involving the liver or lungs, or both, in addition to other organs.[2–4] The disease can remain asymptomatic (90%) but may incidentally result in sudden death.[2–4,7]

Electrocardiographic alterations are not always characteristic of hydatid cysts. However, non-specific disturbances of repolarization, block of the right branch of the bundle of His or atrioventricular node block can occur when the cyst affects the interventricular septum. Septal location of the cyst may cause paroxysmal tachycardia. Cysts lodged in the septum or in the ventricular cavities also cause ventricular arrhythmias. Cysts in the right ventricular cavity may cause right ventricular hypertrophy, whereas those located in the left ventricle usually produce myocardial ischaemia (table 1). Myocardial infarction may occur when the cyst compresses the coronary arteries. Normal electrocardiographic patterns exclude left ventricular wall location.[2,3,6]

Table 1 Clinical manifestations of cardiac hydatidosis *Most frequent clinical manifestations.

Precordial chest pain*
Cough*
Fever
Haemoptysis
Dyspnoea
Anaphylactic shock
Syncope
Arrhythmias and conduction disorders
Acute myocardial infarction
Pericarditis
Valvular dysfunction
Pulmonary hypertension
Pulmonary embolism
Systemic embolism
Sudden death

Echocardiography is the most efficient method of diagnosing hydatid cysts in the heart.[2,7] Chest radiography can demonstrate signs such as pulmonary cyst, altered cardiac silhouette or traces of calcification that suggest a diagnosis of hydatid cyst. Other diagnostic steps to be taken subsequently include CAT and nuclear magnetic resonance. Further complementary examination may include seeking cysts in other locations using computer image techniques and serological tests.[3]

Before operation, cardiac function should be evaluated using cardiac and coronary angiography as preparation for surgical intervention or in case some form of co-existent valvular or ischaemic lesion is present.[5,6]

Surgery requires cardiopulmonary bypass and moderate hypothermia with aortic cross-clamping. One of the difficulties in the removal of the cyst is its location and extreme fragility. If the cyst is ruptured and there is leakage of content into the systemic circulation, an immunological reaction (type 1 Coombs–Gell response) or an alternative pathway of complement activation may occur, with subsequent liberation of substances which can occasionally cause anaphylactic shock.[8,9] The occurrence of this potentially fatal complication may take place during surgery or early in the postoperative course.[10] Another risk of a ruptured cyst is dissemination. For this reason, surgery should be extremely cautious and the cyst must be isolated from the surgical field and sterilized with saline solution[9,11] or other substances such as 2% formalin, 5% silver nitrate solution, 1% iodine solution, 5% cetrimide solution, hydrogen peroxide or 20–30% hypertonic saline solution.[3]

Fatal cases of cerebral air embolism caused by liberation of gas into the circulation have been reported after sterilization with hydrogen peroxide.[12] Hypertonic saline solution is the least toxic, although it is not free of adverse effects as it may cause hypernatraemia and a case of hyperosmolar coma has been reported.[13]

The combination of corticosteroids with H_1 and H_2 blocking agents, and administration of benzodiazepines are thought to be beneficial in preventing the effects of histamine release.[14] The anaesthetic technique should use drugs with minimal histamine-releasing activity. An anaesthetic regimen combining etomidate, vecuronium and fentanyl has proved highly effective.

With pulmonary cysts, high pressure ventilation must be avoided because of the serious risk of cyst rupture; some authors recommend intubation with double-lumen tubes as the most effective method of isolating the affected lung in case of rupture.[13]

Pulmonary artery catheterization is contraindicated in these patients, although no cases of cyst rupture caused by such catheters have been reported. We believe direct insertion of a catheter by the surgeon to monitor left atrial pressure is preferable.

Supraventricular and ventricular arrhythmias may occur frequently as a result of either the cyst itself or surgical excision, before, during or after operation. Patients in whom anaphylactic shock is suspected as a result of cyst rupture require careful preventive treatment with albendazole or mebendazole to prevent dissemination. Follow-up should include periodic check-ups accompanied by serological and imaging tests.[3] Patients with contraindications to surgery should be treated with mebendazole or albendazole, although their efficiency is uncertain.[2 3 5]

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ABSTRACTS

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All authors have certified that, where appropriate, studies have been conducted with the approval of the relevant Human Ethics Committee or Animal Experimental Review Committee.

Anaesthesia with intrathecal ketamine: a dose-finding study

C. R. E. Hawksworth* and M. G. Serpell
Western Infirmary, Glasgow

Intrathecal anaesthesia in the elderly population is associated with a high incidence of significant hypotension.[1] Bion used ketamine as the sole intrathecal anaesthetic agent for lower limb surgery and demonstrated a lack of cardiovascular depression which might be advantageous in this population.[2] We undertook a dose-finding study to determine its usefulness as a sole anaesthetic agent for transurethral prostate and bladder tumour resection.

Ten adult male patients ASA status I–III were recruited. Spinal anaesthesia was performed using a 25-gauge Whitacre needle via the L2/3 or L3/4 spaces. A pre-determined dose of preservative-free ketamine (10 mg ml^{-1}) was injected over a period of 30 s. The patient was then placed supine. Sensory and motor block were assessed by pin-prick and a modified Bromage score respectively. The occurrence of nystagmus, dysphoric symptoms or hallucinations were noted. If an adequate block was not obtained, or the block began to wear off during surgery, a general anaesthetic was administered.

The initial dose of ketamine used was 0.5 mg kg^{-1}. This failed to produce any detectable block. The next patient received 0.75 mg kg^{-1} which produced a successful block. Thereafter, a technique of sequential allocation with incremental changes of 0.05 mg kg^{-1} was used. No significant cardiovascular changes were noted. The other results are shown in table 1.

We concluded that intrathecal ketamine at doses of 0 .7 mg kg^{-1} and above produced a sensory and motor block, but the psychomotor side effects and short duration of action precluded its use as the sole anaesthetic agent for routine transurethral urological surgery.

Key words
Anaesthetics intravenous, ketamine.

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Table 1 Dose of ketamine given, timing of block, and presence of side effects. K=Ketamine, T_{motor}=time of onset of maximum motor block, S_{max}=maximum sensory level achieved, $T_{S_{max}}$= time to S_{max} in minutes, T_{GA}=time general anaesthesia induced, T_{off}=time sensory block wore off, Nyst=nystagmus present, Hall=occurrence of hallucinations

Patient number	K dose (mg kg^{-1})	K dose (mg)	T_{motor} (min)	S_{max}	$T_{S_{max}}$ (min)	T_{GA} (min)	T_{off} (min)	Nyst	Hall
1	0.50	30	—	—	—	11	—	No	No
2	0.75	70	10	L1	20	—	60	Yes	No
3	0.70	40	5	T12	5	—	45	No	No
4	0.75	68	5	T9	5	38	—	Yes	No
5	0.80	48	5	T11	5	30	—	No	Yes
6	0.85	62	5	T12	15	—	60	Yes	No
7	0.85	68	5	T10	15	30	—	Yes	Yes
8	0.90	75	10	L1	15	37	—	No	No
9	0.95	97	5	T7	20	40	—	Yes	Yes
10	0.9	58	5	T11	10	—	45	Yes	No

Effects of low-dose isoflurane on contrast-sensitivity in volunteers

S. R. J. Taylor*, O. A. Khan*, M. Swart* and J. G. Jones
University Department of Anaesthesia, Addenbrooke's Hospital, Hills Road, Cambridge, CB2 2QQ

Many different psychometric tests have been used as a measure of recovery from anaesthesia, including saccadic eye movements and choice-reaction-time tests.[1] However, one test which has not previously been used is contrast sensitivity. We have assessed the effects of isoflurane on subjects' contrast-sensitivity thresholds. This measures the ability of a subject to discern letters from a background when the contrast between the two varies.

Sloan[2] letters were displayed on a high-resolution computer monitor and five healthy subjects were required to indicate which of 10 possible letters they thought had been displayed. Response time was not recorded. An experimental run consisted of 50 such letter trials, displayed in a sequence of pseudo-random contrasts. The resulting data were fitted to the curve

$$P_c=\frac{0.9}{1+(kC)^n}+0.1$$

where P_c indicates the probability of correctly identifying the letter at contrast C, using the Marquardt–Levenberg algorithm, and the contrast at which the subject correctly identified 50% of the letter trials, that is the threshold contrast, was calculated.

Experimental runs were performed for two tests, the first involving the constant appearance of the letter until the subject made his response, and the second flashing the letter onto the screen for $^1/_{72}$ s only (1 frame). These were repeated after the administration of isoflurane in 100% oxygen to achieve an end-tidal concentration of 0.1%.

In all five subjects, administration of isoflurane increased the threshold contrast for both the constant and the flash protocols (fig. 1).

The results showed that isoflurane reduced the contrast sensitivity of the subjects. The dose-dependency of this relationship is currently under investigation.

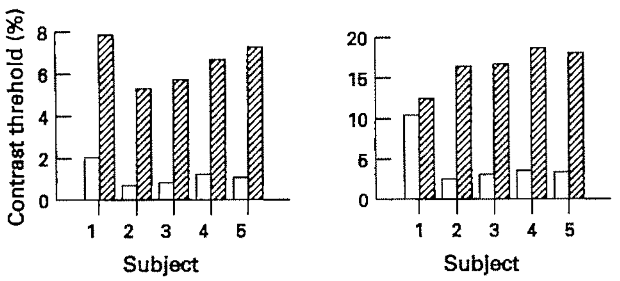

Figure 1 Contrast sensitivity thresholds for the constant letter presentation test (left) and flashed letter test (right) before (open bars) and during (shaded bars) administration of isoflurane to achieve an end-tidal concentration of 0.1%.

Key words
Recovery. Psychometric tests. Anaesthetics, volatile.

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Effects of low-dose isoflurane on inhibition of saccadic eye movement

O. A. Khan*, S. R. J. Taylor*, M. Swart* and J. G. Jones
University Department of Anaesthesia, Addenbrooke's Hospital, Hills Road, Cambridge, CB2 2QQ

Saccadic eye movements have been used as a psychometric measurement of recovery from anaesthesia. For example, the peak velocity of these movements has been shown to be depressed in a dose-dependent manner by a number of inhalation anaesthetic agents, including isoflurane, halothane and cyclopropane.[1 2] We have examined the effects of isoflurane on a hitherto unappraised aspect of saccadic eye movements—namely the ability of subjects to inhibit saccadic eye movements through the use of a countermanded saccadic protocol described below.

Measurements of saccadic eye movements were made by a computer-based system[3] using an infrared oculometer. Subjects were seated 50 cm from a 40 cm rectangular LED display. All trials began with the transient presentation of a central fixation point, and after a variable delay, a target appeared at one of two locations at the extremes of the LED display, signalling the subject to make a saccade to the target. In 50% of the trials, the fixation light then reappeared after a 50 ms delay, signalling that the saccade to the target should be inhibited (the stop signal). For each subject the total number of trials was 200 comprised of 100 stop and 100 test signals. The number of occasions when five healthy volunteers failed to inhibit saccades after stop-signal presentation was recorded under baseline conditions, and after administration of isoflurane in 100% oxygen to achieve an end-tidal concentration of 0.1%.

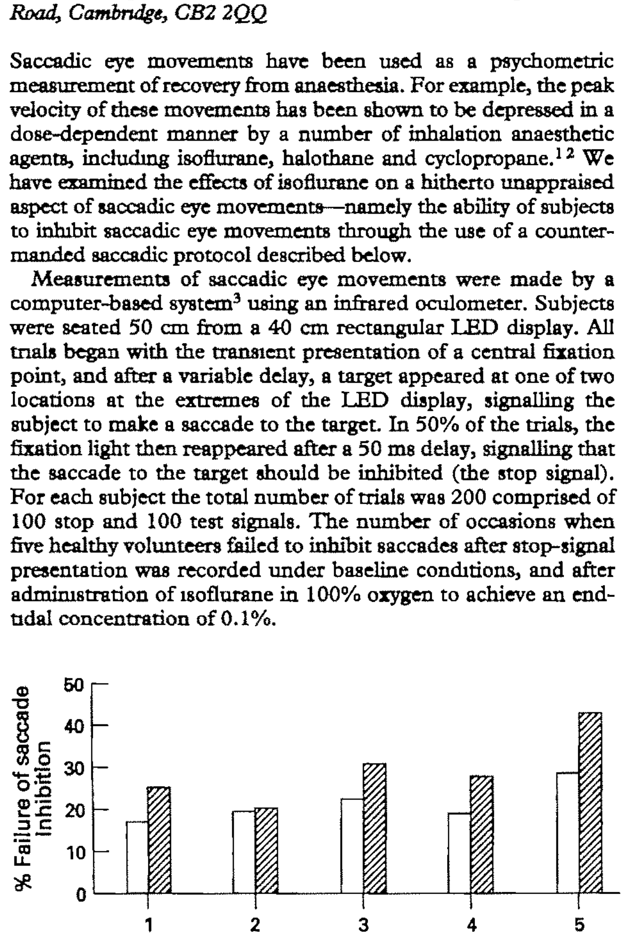

Figure 2 Number of failures to inhibit saccades (as a percentage of total stop signals) under baseline conditions (open boxes) and with isoflurane (hatched boxes) in five subjects.

In all five subjects, administration of isoflurane increased the percentage of occasions when the subjects failed to inhibit saccadic movements after the stop signal (fig. 2).

The results showed that low-dose isoflurane reduced the ability of subjects to inhibit saccades. The dose-dependency of this relationship is currently under investigation.

Acknowledgement

The authors would like to thank Dr. R. H. S Carpenter and Dr. D. P. Hanes for their support and encouragement.

Key words
Recovery. Psychometric tests. Anaesthetics, volatile.

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Outcome of labour using low-dose extradural bupivacaine compared with intramuscular pethidine

P. N. Robinson*, M. Romney*, H. Gordon* and B. A. Loughnan
Departments of Anaesthesia and Obstetrics, Northwick Park Hospital, Middlesex HA1 3UJ

Anaesthetic extradural analgesia is associated with an increased likelihood of obstetric intervention.[1] Current obstetric anaesthetic practice using a weaker solution of local anaesthetic with an opioid is associated with less motor block[2] and may result in a lower incidence of instrumental deliveries. This hypothesis is unproven in the absence of comparison with a non-extradural control. Our study compares the obstetric outcome between primigravidae receiving a "low-dose" extradural mixture and women receiving pethidine.

Written informed consent was obtained from 372 primigravidae in the later stages of uncomplicated pregnancy. Only women uncommitted to any particular form of analgesia were recruited. On admission to the delivery suite in established labour, 110 women opted out of the study, and 71 women required entonox only. A further 38 were excluded. The remaining 153 women were allocated randomly to receive either pethidine 100 mg boluses by i.m. injection (64 patients) or a "low-dose" extradural mixture with fentanyl (89 patients). The extradural regimen consisted of an initial dose of 0.125% bupivacaine 10 ml, and fentanyl 50 μg, with further 10-ml top-ups of a mixture of 0.1% bupivacaine with fentanyl 2 μg ml^{-1}. Rescue analgesia using the same extradural regimen was available to the pethidine group. The management of labour was standardized according to the criteria for the active management of labour.[3] Pain relief scores were assessed 24 h after delivery by the mother on a 5-point verbal rating scale. The main outcomes measured were the mode of delivery and duration of first and second stages. Statistical analysis was performed on the three groups (extradural, pethidine and extradural supplementation of pethidine) using analysis of variance (ANOVA), chi-square test, and Pearson's chi-square test as appropriate.

Twenty-six women in the pethidine group (40.6%) required an extradural for uncontrolled pain. Of those mothers who received pethidine as their sole analgesic in labour, 31 (82%) had a normal vaginal delivery compared with 45 (51%) and 10 (31%) in the extradural and the pethidine plus extradural groups respectively. Mode of delivery was associated with method of analgesia received (chi-square=6.64, $P<0.03$). Use of a "low-dose" extradural was associated with a lower incidence of spontaneous vaginal delivery or low forceps than pethidine alone ($P<0.01$). Those receiving an extradural had the same duration of first and second stages. Mothers receiving an extradural rated their quality of analgesia higher than those receiving pethidine alone ($P<0\ 001$).

Our results suggested that a "low-dose" extradural analgesic technique did not confer any advantage over pethidine in terms of avoiding instrumental delivery or Caesarean section, even when labour is actively managed.

Table 2 Slopes (logit [% gastric emptying] or logit [% geometric centre] per unit log dose) and differences in slopes of the logit curves for the effect of opioids on gastric emptying and gastrointestinal transit of saline. Data for morphine are from a previous study[1]

	Gastric emptying		Gastrointestinal transit	
Drugs	Slopes (95% CL)	*P*	Slopes (95% CL)	*P*
Morphine (n=52)	−1.38 (−1.48, −1.29)		−0.97 (−1.05 , −0.89)	
Nalbuphine (n=36)	−0.48 (−0.55, −0.40)		−0.23 (−0.30, −0.16)	
Pentazocine (n=29)	−1.67 (−1.8, −1.5)		−1.03 (−1.18, −0.88)	
Differences between drugs				
Morphine–nalbuphine	−0.91 (−1.27, −0.55)	<<0.001	−0.74 (−1.05, −0.44)	<<0.001
Morphine–pentazocine	0.29 (−0.28, 0.86)	0.32	0.06 (−0.43, 0.54)	0.82

Acknowledgement

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Key words
Anaesthesia, obstetrics. Anaesthetic techniques, extradural.

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Effects of nalbuphine, pentazocine and U50488H on gastric emptying and gastrointestinal transit in the rat

T. Asai, W. W. Mapleson and I. Power
Department of Anaesthetics and Intensive Care Medicine, University of Wales College of Medicine, Cardiff, and Department of Anaesthesia and Pain Management, University of Sydney, RNSH, St. Leonards, Australia

Morphine markedly inhibited both gastric emptying and gastrointestinal transit to a similar degree in the rat.[1] We studied the effect of mixed agonist–antagonist opioids (nalbuphine and pentazocine) and a kappa opioid agonist (U50488H) on gastric emptying and gastrointestinal transit, and their interactions with morphine.

In each group of five to eight male Wistar rats, nalbuphine (0.01–30 mg kg^{-1}), pentazocine (1–30 mg kg^{-1}), U50488H (1–100 mg kg^{-1}) or saline was injected i.p. at 0 min. Another four groups of rats received morphine 13.4 mg kg^{-1} (ED75) and one of the following substance, all at 1.0 mg kg^{-1}: saline, nalbuphine, pentazocine or U50488H. Radiolabelled saline 1 ml was infused into the stomach at 30 min; and at 1 h the animal was killed, the gastrointestinal tract was removed and the small intestine was divided into 10 equal segments. The radioactivity in the stomach and in each segment of the intestine was counted; gastric emptying and gastrointestinal transit were calculated.[1] Data for morphine were from a previous study.[1] The Mann–Whitney *U* test was used for comparison of substances or combinations of substances. Slopes for dose-response curves were determined using logistic regression of inhibition, with respect to saline, of gastric emptying and of geometric centre on log-dose.

Nalbuphine significantly, but only weakly, delayed gastric emptying ($P<0.0005$) and gastrointestinal transit ($P<0.01$). Pentazocine markedly inhibited both, whereas U50488H did not significantly inhibit either. The slopes of the dose-response curves for nalbuphine, but not for pentazocine, on both gastric emptying and gastrointestinal transit were significantly less steep than those for morphine (table 2). Nalbuphine significantly antagonized the inhibitory effect of morphine on gastric emptying ($P=0.005$) and gastrointestinal transit ($P=0.02$), whereas neither pentazocine nor U50488H significantly did so.

In the rat, nalbuphine, which only weakly inhibited gastric emptying and gastrointestinal transit, antagonized the inhibitory effect of morphine, whereas pentazocine which inhibited both, and U50488H which did not significantly alter either, did not alter the effect of morphine.

Key words
Gastrointestinal tract, emptying. Analgesics, opioid.

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Propofol induction characteristics after fentanyl or midazolam and fentanyl

L. M. Collins*, C. M. Cooney and G. Fitzpatrick
Department of Anaesthesia, Adelaide and Meath Hospital, Dublin 8, Ireland

In a randomized-controlled double-blinded study, we examined the effects of pretreatment with fentanyl or midazolam and fentanyl on induction of anaesthesia with propofol.

Seventy-five ASA I day-surgery patients were allocated randomly to receive either 0.9% saline (group C), fentanyl 1 μg kg^{-1} (group F), or midazolam 0.03 mg kg^{-1} and fentanyl 1 μg kg^{-1} (group MF) 3 min before induction with a sleep dose of propofol. Anaesthesia was maintained with 40% oxygen in nitrous oxide and 3% sevoflurane for 3 min before insertion of a laryngeal mask. Heart rate (HR), mean arterial pressure (MAP) and oxygen saturation (Sp_{O_2}) were recorded at baseline and at 1-min intervals throughout. Pain on injection of propofol and involuntary movements were assessed by a blinded observer. Data were analysed using chi-square test, ANOVA and Student's *t* test as appropriate. Results are presented as mean (SD).

Age, weight, sex and baseline HR, MAP and Sp_{O_2} were similar between groups. In group F and group MF, the dose of propofol was significantly lower than control (table 3). The incidence of pain on injection was significantly lower in group MF and the incidence of involuntary movements was significantly lower in both F and MF groups.

In group MF, Sp_{O_2} decreased from a mean baseline value of 98.2 (1.1)% to 93.76 (3.1)% at 3 min ($p<0.05$). There was no change in Sp_{O_2} in groups F or C. After induction, there was a fall in HR in group F [14 (9.2) beat min^{-1} after 3 min, $P<0.01$] and group MF [8.7 (7.8) beat min^{-1} after 3 min, $P<0.05$]. MAP decreased in group MF before induction [8 (8.5) mm Hg]. After induction, MAP decreased similarly in all groups [group C: 18.3 (14.2) mm Hg; group F: 22.5 (11.5) mm Hg; group MF: 17.2 (10.7) mm Hg].

These findings suggested that fentanyl reduced the induction dose of propofol and lowered the incidence of involuntary movements. Midazolam further reduced propofol requirement,

Table 3 Propofol dose [mean (SD)] and incidence of pain on injection and involuntary movements in the three groups. *$P<0.05$, **$P<0.01$, †$P<0.01$ of fentanyl alone

	Control (*n*=25)	Fentanyl (*n*=25)	Midazolam/ fentanyl (*n*=25)
Propofol dose (mg $kg^{-1)}$	2.76 (0.46)	2.46 (0.42)*	1.99 (0.4)**†
Pain on injection (*n*)	12	10	4*
Movements (*n*)	15	5**	3**

decreased the incidence of pain on injection and in low doses augmented the respiratory depressant effects of fentanyl.

Key words
Hypnotics benzodiazepines, midazolam. Anaesthetics i.v., propofol.

Local anaesthetic agents inhibit [^{3}H] noradrenaline uptake into SH-SY5Y human neuroblastoma cells

P. I. Joyce*, R. Atcheson and D. G. Lambert
University Department of Anaesthesia, Leicester Royal Infirmary, Leicester LE1 5WW

Complex regional pain syndrome type-1 (or reflex sympathetic dystrophy) may occur via sympathetic hyperactivity and is often treated by producing a "chemical" sympathectomy using guanethidine.[1] Guanethidine is taken up via the neuronal catecholamine uptake transporter, uptake-1 [2] and a local anaesthetic is co-administered to reduce the discomfort of the injection. The efficacy of this treatment has been questioned.[3] We hypothesized that the local anaesthetic agent may be inhibiting uptake-1 and hence the uptake of guanethidine. In this study we have examined the effects of a range of local anaesthetic agents on [^{3}H] noradrenaline ([^{3}H]NA) uptake into SH-SY5Y cells that express uptake-1.

SH-SY5Y cells were preincubated in 0.5 ml volumes of Krebs-HEPES buffer, pH7.4 for 15 min in the absence and presence of lignocaine (3 μmol litre^{-1}–10 mmol litre^{-1}), prilocaine, bupivacaine, procaine and dibucaine (10 mmol litre^{-1}). [^{3}H]NA/unlabelled NA (approximately 10–1000 nmol litre^{-1}) was added and the reaction continued for a further 5 min. Reactions were terminated by rapid vacuum filtration. Non-specific uptake was defined in the presence of 10 μmol litre^{-1} imipramine. Data are mean (SEM).

Lignocaine produced a dose-dependent inhibition of [^{3}H]NA uptake with a pIC$_{50}$ of 2.97 (0.01) (1.07 mmol litre^{-1}). Lignocaine (10 mmol litre^{-1}) reduced the maximum velocity of uptake (V_{max}) without affecting the K_m (Michaelis–Menten constant equivalent to half of the maximum velocity) consistent with non-competitive inhibition. (Table 4). Prilocaine, bupivacaine, procaine and dibucaine at 10 mmol litre^{-1} produced >95% inhibition of uptake.

Table 4 Effect of 10 mmol litre^{-1} lignocaine on the K_m and V_{max} for [^{3}H]NA uptake into SH- SY5Y cells. Values were obtained using a double-reciprocal plot of 1/v against 1/[S]

	Number	Control	+Lignocaine	*P*
K_m (μmol litre^{-1})	6	0.70 (0.17)	0.53 (0.11)	>0 05
V_{max} (pmol mm^{-1} mg^{-1} protein)	6	6.61 (1.56)	2.71 (0.49)	<0.05

In this study we have demonstrated that a range of local anaesthetic agents inhibited the uptake of [^{3}H]NA and would therefore be expected to inhibit the uptake of guanethidine when co-administered. Based on a simple bench study in volunteers of varying body size we estimated that 0.5% lignocaine (18.5 mmol litre^{-1}) when injected into an arm would be diluted approximately 17-fold. Assuming homogenous distribution this would yield an "in the arm" concentration of around 1 mmol litre^{-1}, the IC$_{50}$ reported here.

Key words
Sympathetic nervous system, catecholamines. Anaesthetics, local. Pain, chronic.

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Comparison of two steady state-auditory-evoked response methods for assessing depth of anaesthesia in routine clinical practice

M. L. Swart,* J. J. W. M. Stevens,* J. Risdall* and J. G. Jones
University Department of Anaesthesia, Addenbrooke's Hospital, Cambridge CB2 2QQ

The transient and the steady state auditory-evoked response (AER) both reflect changes in depth of anaesthesia but a high proportion of transient AER data has to be rejected (19 of 35 patients) [1] in awake subjects. We examined the effects of general anaesthesia on two steady state AER methods in 18 patients scheduled for gynaecological or general surgery before and during general anaesthesia. The steady state AER was measured as described previously.[2] In addition to measurements of the coherent frequency (CF) we examined the effect of the auditory stimulating frequency on the power in the first harmonic of the EEG after signal averaging and Fourier transformation. We had previously shown that the steady state AER threshold for loss of consciousness was 27 Hz.[3] Of the 42 measurements of CF obtained before anaesthesia, six decreased to below the 27 Hz threshold (Fig. 3A). However if the mean value for CF was derived for each patient then only one patient had a value below 27 Hz. The power in the first harmonic decreased with increasing auditory stimulating frequency and in the awake subjects the threshold frequency for insignificant harmonic power (FIHP) was at a stimulating frequency greater than 40 Hz . There was only one data point (17 Hz) below 40 Hz (Fig. 3A). During anaesthesia

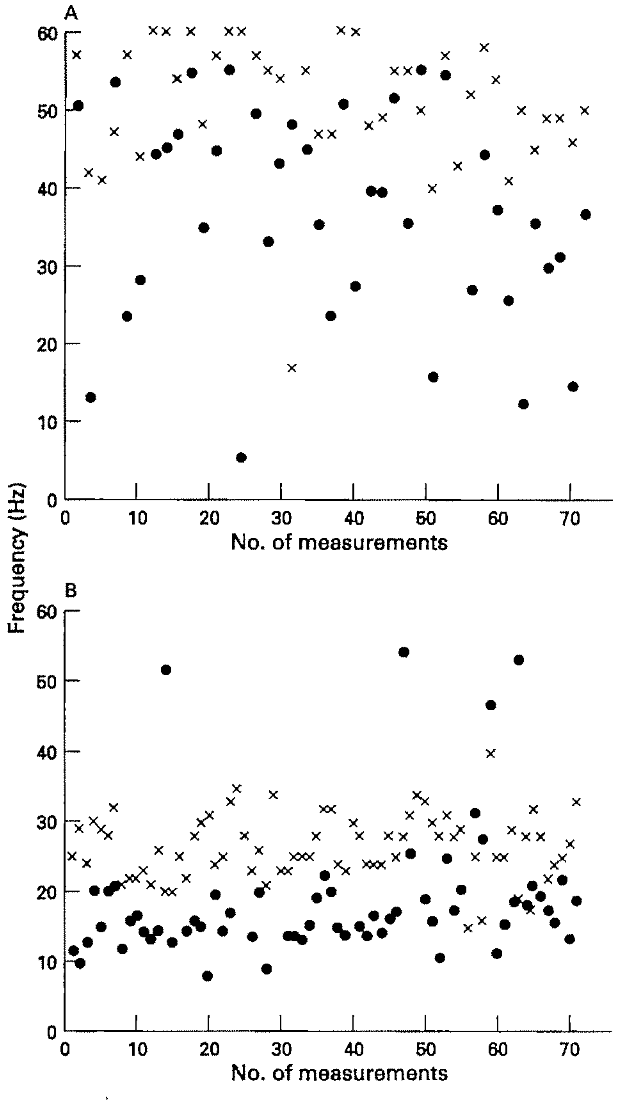

Figure 3 (A) Awake CF (●) FIHP (X). (B) Anaesthetized CF (●) FIHP (X).

(Fig. 3B) there were 71 data points for CF, nine occurring above the 27 Hz threshold. Again when the mean value for each subject was calculated four subjects were above 27 Hz. In the case of FIHP during anaesthesia all but one of the data points were below 33 Hz.

In conclusion, both steady state methods discriminated between the awake and anaesthetized state but the FIHP was a more reliable index than CF.

Key words
Anaesthesia, depth.

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Use of microalbuminuria as an indicator for the development of sepsis and multiple system organ failure

K. L. MACKINNON[*], Z. MOLNAR[*,†], I. D. WATSON[*], E. SHEARER[†] AND D. LOWE[*,‡]
Department of Clinical Chemistry, [†]Intensive Care Unit, [‡]Clinical Audit Department, Fazakerley Hospital, Liverpool L9 7AL

Mortality in the Intensive Care Unit (ICU) is approximately 30%, half of whom die of sepsis and multiple system organ failure (MSOF).[1] Microalbuminuria has been shown to be a non-specific but sensitive marker of systemic inflammation with a more rapid onset than other common inflammatory markers.[2] We investigated the use of microalbuminuria as an indicator of the development of sepsis and MSOF and compared this with other acute phase markers (C-reactive protein and erythrocyte sedimentation rate) over three days.

Fifty critically ill patients in the ICU were recruited to the study after informed agreement from relatives. Blood samples were collected upon admission and daily for up to three days for the determination of C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) by immunoturbidimetry[3] and the Westergren technique[4] respectively. Urine samples were collected every 6 h for 18 h and the microalbumin:creatinine ratio determined by immunoturbidimetry and Jaffé reaction.[5] To assess the progress of organ dysfunction, multiple organ dysfunction scores (MODS) were obtained daily up to a maximum of 10 days.[6] For statistical analysis, Mann–Whitney and chi-square tests were used as appropriate.

Outcome was assessed according to patient survival (survivors, n=36;non-survivors, n=14). ESR and CRP values obtained throughout the study did not show any association with outcome in either group. Microalbumin:creatinine ratios (reference range <3.5 mg:mmol) obtained within 6–12 h of admission were significantly different (survivors:median (m)=3.3, interquartile range (r)=1–14;non-survivors:m=22, r=3–54;p<0.01). Microalbuminuria concentrations were in concordance with the MODS on day 1 (p<0.002).

We concluded that micoralbuminuria measurements can be used to identify high-risk patients, the earlier identification of these patients means that they can be targeted more accurately with more aggressive clinical intervention.

Key words
Measurement techniques, microalbuminuria. Infection, sepsis.

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N-acetylcysteine in multisystem organ failure

Z. MOLNAR[*], E. SHEARER AND D. LOWE[*,‡]
Intensive Care Unit; [‡]Clinical Audit Department; Fazakerley Hospital, Liverpool

Multisystem organ failure (MSOF) remains the biggest challenge in intensive care, and carries a high mortality. The aim of this study was to investigate the effects of *N*-acetylcysteine (NAC), a free-radical scavenger, on mortality and the development of MSOF, when given as a prophylactic treatment to critically ill patients.

After obtaining ethics committee approval, every critically ill patient admitted to our intensive care unit over a 12-month period was entered to the study and a written informed agreement from their relatives was obtained. Those, who had chronic organ insufficiency according to the APACHE II guidelines, and those with isolated head injury or drug overdose were excluded from this randomized, double-blinded, placebo-controlled trial. Patients received either NAC (150 mg kg^{-1} bolus followed by 12 mg kg^{-1} 24 h^{-1}) or the equal volume of placebo (30 ml h^{-1} of 5% dextrose) for a minimum of three up to a maximum of five days. To assess the effects of the treatment on organ function, a multiple organ dysfunction score (MODS) was obtained daily up to a maximum of 10 days.[1] For statistical analysis Mann–Whitney and chi-square tests were used as appropriate.

Of the 86 patients studied 41 received NAC and 45 were given placebo. Age (NAC: median (m)=62, interquartile range (r)=41–69; control: m=63, r=45–73) APACHE II scores (NAC: m=22, r=16–29; control: m=22, r =16–28) and MODS (NAC: m=5, r=4–8; control: m=6, r=4–7) were similar in both groups on admission. Outcome was assessed on leaving the hospital. Mortality rate was 39% in the NAC treated patients, and 29% in the control group but the difference did not achieve statistical significance (P=0.32; 95% CI for mortality differences =−10 to 30%). The progress of the MSOF showed a similar pattern in both groups as indicated by the MODS on day 3 (NAC: m=6, r=3.5–8; control: m=5, r=4–7), and on the final day of assessment (NAC: m=5, r=3–10; control: m=4, r=2–7.5). Regarding the effect of NAC on the cardiovascular, respiratory, renal, liver and haematological systems the changes in the individual organ dysfunction scores were compared using the MODS system, but no statistically significant differences were found.

The role of antioxidants in the treatment of critical illness is unclear. Our prospective, controlled study on 86 patients showed, that NAC treatment at the given dose had no positive effect on outcome, did not improve organ function or the progress of MSOF as indicated by the MODS system.

Key words
Pharmacology, *N*-Acetylcysteine. Complications, multisystem organ failure.

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Midazolam and propofol affect interleukin-8 release from human neutrophils at the post-translational level

H. F. GALLEY AND N. R. WEBSTER
Academic Unit of Anaesthesia and Intensive Care, University of Aberdeen, AB25 2ZD

Interleukin-8 (IL-8) is a potent neutrophil chemotactic and activating factor produced by many different cells, including neutrophils themselves, in response to pro-inflammatory stimuli, via G-protein coupled signal transduction pathways. Both propofol and midazolam have been shown to suppress neutrophil respiratory burst, polarization and chemotaxis.

We have shown recently that the i.v. anaesthetic/sedative agents, propofol and midazolam, suppress the extracellular accumulation of IL-8 from lipopolysaccharide (LPS)-stimulated human neutrophils.[1] Northern analysis with molecular imaging also revealed increased IL-8 mRNA concentrations in the presence of both midazolam and propofol, indicating that transcription of IL-8 mRNA is unaffected. However, the effect on translational processing was unknown. We therefore determined the *in vitro* effect of propofol and midazolam on intracellular IL-8 in isolated human neutrophils. Polymorphonuclear leucocytes were isolated using a single density gradient system, and were incubated with 2 μg ml^{-1} LPS in the presence of propofol or midazolam (1–20 μmol litre^{-1}), or appropriate solvent blanks for 20 h. Interleukin-8 was measured in both supernatants and cell lysates using enzyme immunoassay. Cell protein content was measured using a modified Lowry technique.

As previously, extracellular IL-8 accumulation was decreased dose-dependently by both midazolam (P=0.025) and propofol (P=0.028, Kruskal–Wallis ANOVA). Intracellular IL-8 concentrations increased on exposure to LPS (P=0.05 and P=0.028 for midazolam and propofol respectively, Mann–Whitney U test) and remained increased in the presence of both anaesthetics (fig. 4). These data strongly suggested that the anaesthetic agents exerted their effects at a post-translational level via modulation of transport or secretion of the IL-8 protein from the cell.

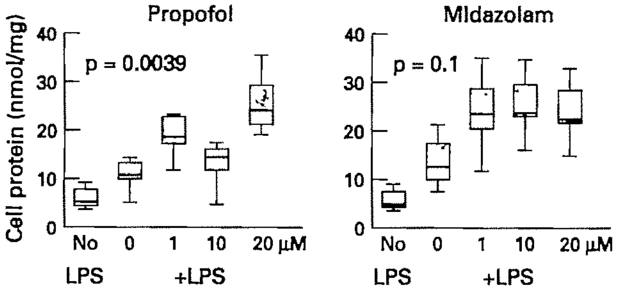

Figure 4 Effect of anaesthetics on intracellular IL-8 concentration in LPS stimulated human neutrophils. Box and whisker plots show median, 25th and 75th percentiles and ranges. *P* values refer to Kruskal–Wallis ANOVA. (n=6–8).

Key words
Interleukin-8. Anaesthetics.

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Effects of a single dose of etomidate on adreno-cortical function in the critically ill

A. R. ABSALOM*, D. R. PLEDGER* AND A. KONG*
Department of Anaesthesia, Ipswich Hospital, Ipswich, Suffolk IP1 5PD

Many anaesthetists still use etomidate for induction of anaesthesia in the critically ill, judging that the benefits of cardiovascular stability outweigh the risks of adrenal suppression. The adrenal effects of single doses have been investigated in healthy patients,[1 2] but not in the critically ill. In this study we compared adrenocortical function after induction of anaesthesia with etomidate or thiopentone in critically ill patients.

The study was approved by the local ethics committee. Thirty-five critically ill adults who needed a general anaesthetic were studied. To be included they had to be ASA grade III or worse, and be considered to be critically ill and requiring admission to the intensive care unit. Exclusion criteria were: known adrenal impairment, allergy to relevant drugs and a history of corticosteroid supplementation in the previous six months. Patients were allocated randomly to receive either etomidate (17 patients) or thiopentone (18 patients) for induction. Before induction blood was taken for a baseline cortisol assay. Twenty-four hours later adreno-cortical function was assessed by performing a short synacthen test—an increase in the cortisol concentration of 200 nmol litre^{-1} or more 30 min after injection of synacthen was regarded as a normal response.

There were no statistically significant differences between the groups in terms of age, sex, APACHE II score and baseline and 24-h (pre-synacthen) cortisol concentrations. Patients anaesthetized with etomidate were more likely (P<0.001, Fisher's exact test) to have an impaired response to synacthen (table 5). The mean (SEM) response in the etomidate group was an increase of 97 (27) nmol litre^{-1}, whereas in the thiopentone group the mean (SEM) increase was 237 (25) nmol litre^{-1}; this difference is highly significant (P<0.001, Wilcoxon rank sum test).

In critically ill patients a single dose of etomidate was associated with at least 24 h of adreno-cortical suppression.

Table 5 Results of short synacthen tests (SST)

Agent	Abnormal SST	Normal SST	Total
Thiopentone	5	12	17
Etomidate	15	2	17
Total	20	14	34

Key words
Anaesthetics i.v., etomidate. Hormones, adrenal.

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Lanz tube as alternative for ICU hyperbaric oxygen therapy

Z. MOLNAR* AND P. CHARTERS
NW Emergency Recompression Unit/ Department of Anaesthesia, Aintree Hospitals, Liverpool

Tracheal tubes cuffs during intensive care unit (ICU) hyperbaric oxygen treatments need to resist pressures equivalent to 3ATA. Saline filled or sponge foam cuffs (for example, Bivona) are recommended.[1] The foam cuff requires a good fit in the trachea and overinflation with saline may risk tracheal injury. For high volume, low pressure cuffs, maintenance pressures of 25–30 cm H_2O are desirable.[2] The Lanz tracheal tube was considered worthy of investigation as an alternative.

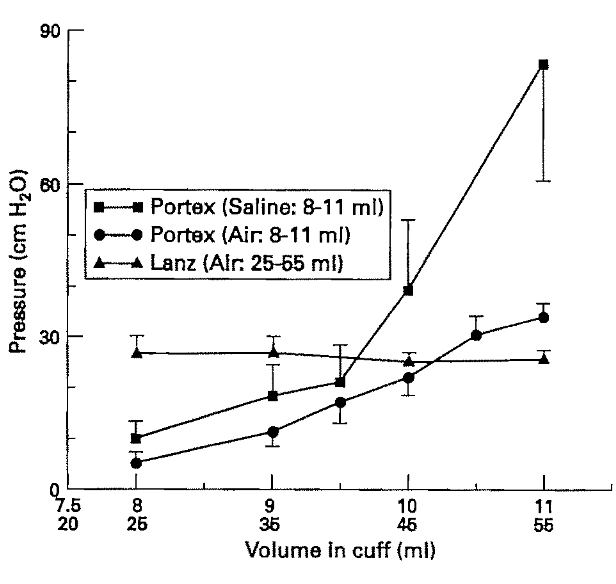

Figure 5 Effect of cuff volume on cuff pressure. (Measured at surface pressure). Four tracheal tubes per study and two model tracheas (i.e. points mean of eight measurements).

Model tracheas 20 mm in diameter with elastic posterior walls were constructed.[3] At normal surface pressure, they were intubated with size 8.0 Portex tubes inflated with either air (as control) or saline in increments, or size 8.0 Lanz tubes inflated with air (fig. 5). Cuff pressures were monitored with a fluid manometer or pressure transducer attached to the valve of the pilot tubes. The Lanz tubes had stopcocks inserted in their valves. Ability to maintain cuff pressure during hyperbaric conditions was then tested. Two Lanz cuffs were inflated with 60 ml of air and in two others 90 ml of air was used after removal of the outer restricting envelope. Cuff pressures were recorded at surface, 6.1, 12.2, 27.4 and 50.3 metres depth.

The Lanz gave steady cuff pressures for cuff volumes 25 to 55 ml. As expected, there was a sudden overpressure in the saline filled cuffs. Under hyperbaric conditions, the Lanz performed as might be expected from Boyle's law. A cuff filled to 60 ml at surface provided steady pressures down to 12.2 metres only. When the inflating balloon was initially inflated to 90 ml, the pressure was lower than for the normal working range. Hysteresis was unimportant.

A Lanz cuff has potential as an alternative to saline filled cuffs. A balloon capacity of 90 ml (with modified valve) should cover normal therapeutic requirements.

Key words

Equipment, cuffs, tracheal. Hyperbaria.

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Optimal brain tissue oxygenation during hyperventilation in patients with head injuries: measured by a multiparameter sensor

S. GUPTA* [1], M. L. SWART*[1], P. AL-RAWI* [3], P. HUTCHINSON*3, D. K. MENON[1,2] AND A. K. GUPTA [1,2]
Departments of Anaesthesia[1], Neuro Critical Care[2] and Neurosurgery[3], Addenbrooke's Hospital, Hills Road, Cambridge CB2 2QQ

The benefit of hyperventilation as a method for reducing increased intracranial pressure (ICP) was first demonstrated by Lundberg and colleagues in 1959.[1] However, more recently its use has become controversial mainly because of the risk of decreasing cerebral blood flow to the point of ischaemia.[2] Currently, measurement of cerebral oxygenation and metabolism in patients with head injury rely on indirect methods. In this study, we have used a new multiparameter sensor originally designed for continuous intra-arterial blood-gas measurement, to measure the brain tissue oxygen (PTi_{O_2}), carbon dioxide (PTi_{CO_2}), pH and temperature. Our aim was to identify the range of Pa_{CO_2} at which PTi_{O_2} is optimal.

After informed consent from the relatives of the patients, 10 patients presenting with severe head injury were studied. The sensor (Paratrend 7, Diametrix Medical, High Wycombe, U.K.) was inserted through an adapted Camino bolt into the brain tissue on the side of injury. Invasive arterial pressure, intracranial pressure, jugular bulb venous saturation (Sj_{O_2}) and arterial blood-gases were continuously monitored. Initial readings of PTi_{O_2}, PTi_{CO_2} and pH were recorded at a baseline Pa_{CO_2} of 4.5 to 5.0 kPa. The Pa_{CO_2} was then decreased in a stepwise manner to 3.0 kPa. If the Sj_{O_2} decreased to less than 50%, hyperventilation was abandoned.

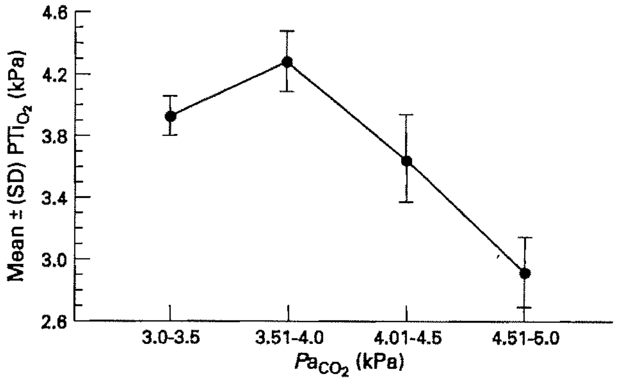

Figure 6 Effect of Pa_{CO_2} on PTi_{O_2}.

There was no significant change in the patient's body and brain temperature, Pa_{O_2} and cerebral perfusion pressure. PTi_{CO_2} decreased with a reduction in Pa_{CO_2}. There was little change in brain pH. When the data are pooled as shown in fig. 6, optimal PTi_{O_2} occurs in the Pa_{CO_2} range of 3.5–4.0 kPa. PTi_{O_2} was significantly higher between 3.5 and 4.0 kPa Pa_{CO_2} compared with baseline ($P<0.0001$).

PTi_{O_2} was optimal between a Pa_{CO_2} of 3.5 and 4.0 kPa. This range is narrower than the previously published range.[3]

Key words

Complications, head injury. Hyperventilation.

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Accurate measurement of "true glottic view"

P. GROOM* AND P. CHARTERS
Department of Anaesthesia, Aintree Hospitals, Liverpool

Previous attempts at measuring accurately the view at laryngoscopy described the "true glottic view" in terms of multiple "restricted windows".[1] Two "windows" are especially important: the "reference" window, where the upper incisors are aligned with the posterior glottis and the "vanishing point", the most anterior

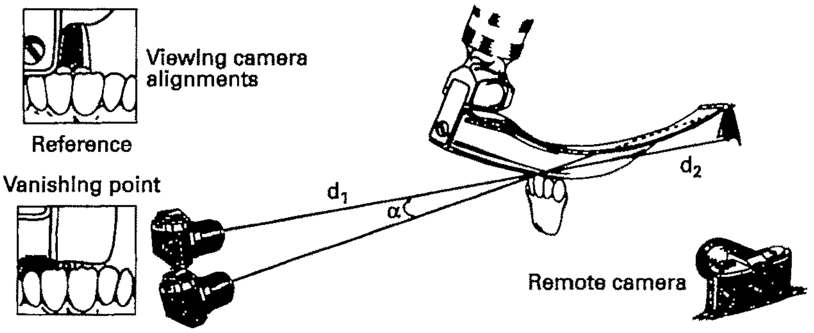

Figure 7 Model simulation.

part of the glottis visible. Restricted window photographs require special considerations because of out of focus magnification phenomena. The introduction of a remote camera eliminated this problem and a novel trigonometric method of indirectly assessing true glottic view evolved as a result. This new method is inherently simpler and refining accuracy is straightforward.

Fixed focus imaging by a single medical photographer was checked for consistency. In a model simulation (fig. 7), if the focusing distance is known, the incisor-glottis distance (d_2) can be estimated by subtracting the camera-incisor distance (d_1).The viewing camera "panning angle" (α) was determined from sequential imaging of the reference and vanishing point alignments by the remote camera. True glottic view is calculated as $2.d_2.(\sin \alpha/2)$. The direct model value for true glottic view is the distance up from the posterior glottis to the intersection with a tangent from the incisor along the blade's lingual surface.

The 95% confidence interval for the fixed focal distance (10 observations) was 57.77 (±0.85) cm. The limits of agreement for the true glottic view were: −0.28 to 0.19 cm. Further refinements are anticipated and an accuracy of ±0.1cm at full glottic exposure should be feasible.

Key words
Anaesthetic techniques, laryngoscopy. Model, stimulation.

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Respiratory complications associated with tracheal intubation and extubation

K. Koga*, T. Asai, C. McBeth* and R. S. Vaughan*
Department of Anaesthetics and Intensive Care Medicine, University Hospital of Wales, Cardiff

Several respiratory complications may occur during tracheal intubation and extubation, but the incidence of these is not clear. Therefore, we studied these incidences.

In a prospective manner, we conducted a survey regarding the incidence of complications associated with tracheal intubation and extubation. The data sheet was designed to obtain the following: the view of the oropharynx (Mallampati score); respiratory complications during induction of anaesthesia; the view of the glottis at laryngoscopy (Cormack and Lehane's score); respiratory complications at tracheal extubation and in the recovery room. Anaesthetists were asked to obtain data during anaesthesia from all patients who underwent elective surgery and in whom the trachea was intubated. Data were not obtained when the patient was transferred to the intensive care unit before tracheal extubation, or when tracheostomy was performed during operation. Nurses were asked to fill in the data sheet for the events in the recovery room. If there were omissions, an investigator contacted the anaesthetist or nurse and rectified the omission.

There were 1200 patients who were subjects for the survey during a 4-month period. We collected data from 1011 patients, but the data from six patients were incomplete. Therefore, data from 1005 patients were used for analysis (collection rate: 83.8%). Respiratory complications occurred in 46 patients (4.6%) during induction of anaesthesia (table 6). Complications occurred immediately after tracheal extubation in 74 patients (7.4%) and in the recovery room in 95 patients (9.5%) (table 6), with a total of one or more incidents after tracheal extubation in 154 of 1005 patients (15.3%).

The incidence of respiratory complications associated with tracheal extubation were comparable to, or even higher than, that during tracheal intubation.

Key words
Complications, postoperative. Intubation, tracheal.

Predicting the moisture-conserving performance of breathing system filters with different anaesthetic breathing systems

A. R. Wilkes* and J. S. Mecklenburgh
Department of Anaesthetics and Intensive Care Medicine, University of Wales College of Medicine, Cardiff CF4 4XN

Breathing system filters (BSF) are recommended for use in anaesthesia to reduce the risk of cross-infection.[1] When placed at the Y-piece, a BSF acts as a heat and moisture exchanger (HME), reducing the moisture loss from the patient. According to the international standard for HME,[2] the moisture-conserving performance is determined by using dry gas on the machine side of the device under test. However, with some anaesthetic breathing systems, the gas in the breathing system (BSG) will be at least partly humidified. This will further reduce the loss of moisture from the patient. The extent of this reduction was investigated by measuring the moisture loss from a patient model.

The patient model "breathed" spontaneously (0.5 L V_T, 20 beats min^{-1}, 1:2 I:E ratio), expiring fully saturated gas at 34°C (moisture content 37.7 mg $litre^{-1}$). Three each of four different BSF were tested. The BSF was connected to the patient model. A T-piece was connected to the machine side of the BSF and humidified air passed through the T-piece at 45 litre min^{-1}, a flow greater than the predicted inspiratory flow. This humidified air represented BSG. Three different humidity levels of BSG were generated (mean (SD) 7.2 (0.2), 12.6 (0.3) and 19.2 (0.3) mg $litre^{-1}$) and the net moisture loss from the patient model was measured gravimetrically over 2 h for each level. The same levels were used for each BSF in increasing order of humidity, after a 1-h stabilization period at the lowest humidity level of BSG.

The measured moisture loss from the four BSFs varied from 1.8 to 14.8 mg $litre^{-1}$ depending on the device and the moisture content. Moisture loss was related to moisture content of the BSG by the equation:

$$l_c = l_o - \frac{c}{31}(l_o - 1)$$

where l_c is the net moisture loss from the patient model (mg $litre^{-1}$), c is the moisture content of the BSG (mg $litre^{-1}$), l_o is the moisture loss when $c=0$.

The mean (SD) difference (predicted−actual) was −0.08 (0.27) mg $litre^{-1}$. l_o is obtained when determining the performance of HME according to ISO 9360. Values of l_o are published in the Medical Devices Agency's series *Evaluation* Values of c for various breathing systems are available.[3] The moisture-conserving performance of BSF can therefore be predicted readily when the BSF is used with different anaesthetic breathing systems.

Table 6 Ranked incidence (percentage and 95% confidence limits [CL]) of specific respiratory complications and total of any one or more complications associated with tracheal intubation and extubation

During induction of anaesthesia		Immediately after extubation		In the recovery room	
Coughing	1.5	Desaturation (<90%)	2.4	Airway obstruction	3.8
Difficult ventilation	1.4	Breath-holding	2.0	Coughing	3.1
Desaturation (<90%)	1.1	Airway obstruction	1.9	Desaturation (<90%)	2.2
Difficult intubation	0.8	Laryngospasm	1.7	Laryngobronchospasm	1.0
Laryngospasm	0.4	Apnoea, hypoventilation	0.9	Apnoea, hypoventilation	0 8
Oesophageal intubation	0.3	Inadequate reversal	0.5	Vomiting	0.7
Gagging	0.1	Vomiting	0.3	Breath-holding	0.3
		Masseter spasm	0.1	Inadequate reversal	0.3
Total of one or more	4.6		7.4		9.5
95% CL	[3.3,5.9]		[5.7,9.0]		[7.6,11.3]

Acknowledgement

This work resulted from the investigation of the performance of HMEs for the Medical Devices Agency.

Key words
Complications, humidification. Equipment, heat and moisture exchanger.

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Artificial neural networks for distinguishing disturbed from undisturbed breathing

P. Caleb*, P. K. Sharpe*, A. Black and C. Day
Intelligent Computer Systems Centre, University of the West of England and Department of Anaesthesia, Bristol Royal Infirmary

If breathing pattern, as monitored by respiratory inductance plethysmography, contains information on the likelihood of imminent cessation of spontaneous breathing in patients receiving potent analgesic treatments, any such information is probably contained in periods of quiet breathing rather than in periods of disturbance from talking, coughing, bodily movement, etc. We explored the feasibility of using artificial neural networks [1] for automating the distinction of undisturbed from disturbed breathing in signals of ribcage movement from five patients who had been monitored overnight after various types of surgery. A difficulty is to establish the range of what constitutes undisturbed breathing.

Trial and error identified four useful features of breathing pattern that were extractable from 30-s samples of processed signal (CED 1401, Cambridge Electronic Design Ltd): (i) the number of peaks, (ii) the variability of the inter-peak interval, (iii) the "straightened length" of the signal and (iv) the accumulated absolute difference between adjacent peaks. For an exploration of supervised learning, the features were extracted from 30 segments of breathing from one patient: these had been labelled by eye as "undisturbed". The multivariate normal distribution of the four features was estimated and the set of undisturbed exemplars was expanded five times by bootstraping. A set of 5 multilayer perceptrons (MLPs: Graphical Interface for Multiple Neural Networks package) was trained by error back-propagation to recognize as "disturbed" any segment of breathing pattern whose features were more than 3 SD from the centroid of undisturbed features. Each MLP had four input, two hidden and one output nodes. The set used a majority voting system to classify two fresh sets of pre-labelled exemplars, one from the same patient and another from a different one. The best criterion for discrimination gave 100% sensitivity and 94% specificity on data from the same patient, and 88% sensitivity and 95% specificity on data from the other patient. The tedium, labour and uncertainty in pre-labelling training and test segments curtailed further exploration. As an alternative to pre-labelling each individual segment by eye, we also explored unsupervised learning in a self-organizing map or Kohonen network. Nine hours of signal (three from each of three patients) were used with the SOM-PAK package (University of Helsinki) to train self-organizing maps to recognize clusters of features and map them on to a 7 x 4 hexagonal lattice along with the trajectory of successive segments. The visually recognisable affinities (permutations and combinations of baseline disturbance, regular or irregular, fast or slow) between segments of pattern that mapped to different parts of the lattice were then used to label the map. The map was tested using fresh segments of breathing from the three patients whose patterns had been used in the training and from the two whose patterns had not. The fresh segments appeared to be placed in the appropriate regions of the map.

A combination of SOM and MLP appeared worthy of further study.

Key words
Measurement techniques, neural network, artificial. Ventilation, pattern.

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Estimation of cardiac output using the Maxima breathing system

***D. M. Miller, *J. Greef and *J. A. Wessels**
Department of Anaesthesiology, Tygerberg Hospital, 7505, South Africa

The Maxima is a new breathing system which is used as a rebreathing system in controlled ventilation with the selective elimination of alveolar gas.[1] Under these conditions, effective

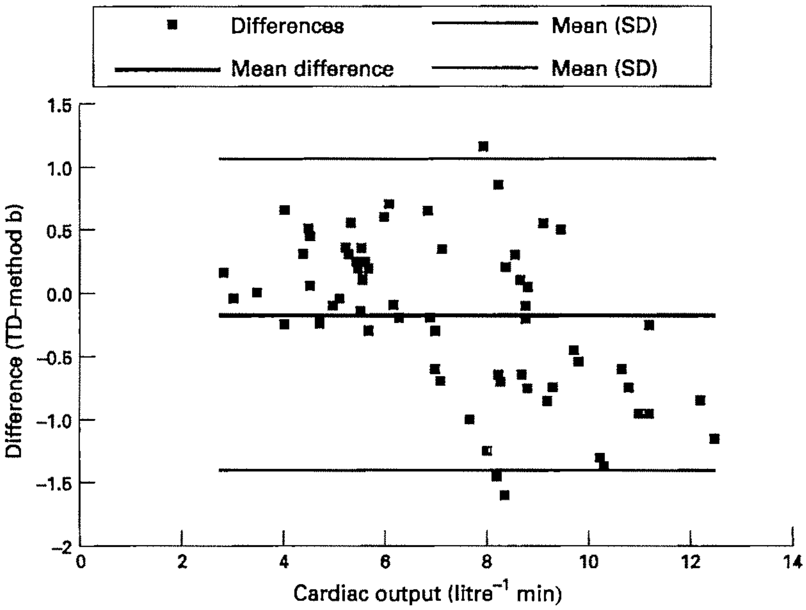

Figure 8 Bland and Altman plot of pulmonary blood flow estimates (two for each subject) according to method (b) against the thermodilution method (TD).

alveolar ventilation is equal to the fresh gas flow ($\dot{V}F$). Without the need for a mixing chamber, "mixed" eliminated carbon dioxide ($F\bar{E}_{CO_2}$) may be measured directly. With steady state conditions, and assuming a respiratory quotient of 1, carbon dioxide production ($\dot{V}_{CO_2}$)$=\dot{V}F\times\bar{E}F_{CO_2}$. The non-direct Fick principle applied to carbon dioxide exchange ($\dot{Q}=\dot{V}_{CO_2}$/pulmonary venous to artery carbon dioxide content difference ($Ca_{CO_2}-C\bar{v}_{CO_2}$) may be modified to $\dot{Q}=\dot{V}F\times F\bar{E}_{CO_2}/(Ca_{CO_2}-C\bar{v}_{CO_2})$. If $\dot{V}F$ in the breathing system is adjusted so that $F\bar{E}_{CO_2}$ is equal to ($Ca_{CO_2}-C\bar{v}_{CO_2}$, then $\dot{Q}=\dot{V}F$. It has been shown that $\dot{Q}=\dot{V}F$, when $\dot{V}F$ is adjusted to achieve an $F<_{CO_2}$ value of approximately 4.1 kPa [equivalent to a ($Ca_{CO_2}-C\bar{v}_{CO_2}$) value of 4.1 ml dl^{-1}].[2] This was demonstrated in a pilot study using nine patients with haemoglobin concentrations (Hb) >10 g dl^{-1}, general anaesthesia and septicaemia with high output in the Intensive Care Unit (ICU).[2] The inaccuracy level was 9%, bias −0.05% and correlation coefficient r=0.94.[2]

This study extended the application within the ICU setting to include a wide variety of conditions all requiring ventilation and haemodynamic monitoring and no limitation was placed on Hb values (mean value=11.5, range 6.2–15.5 g dl^{-1}). Cardiac output was estimated using a thermodilution (TD) technique in 33 patients, all in the ICU except for five who were evaluated during general anaesthesia. Cardiac outputs were estimated using information from (a) $\dot{V}_{CO_2}$ measurements and (b) $\dot{V}_{CO_2}$ and Hb. The results with respective methods (a) and (b) applied to the 33 subjects yielded a correlation with TD measurements—coefficient r=0.9 and 0.91 with a bias of −13% and −4% and inaccuracy of 15% and 14% (fig. 8).

Key words
Equipment, Maxima breathing system. Monitoring, cardiac output.

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Comparison of neuromuscular blocking effects and train-of-four fade of cisatracurium with other blocking agents

M. T. CARROLL*, D. LOWRY*, R. K. MIRAKHUR AND K. C. MCCOURT*
Department of Anaesthetics, The Queen's University of Belfast, Belfast BT9 7BL

Cisatracurium is a recently introduced intermediate duration non-depolarizing neuromuscular blocking drug with a potency approximately three to four times that of atracurium.[1] It has also been shown previously that different neuromuscular blocking agents exhibit different degrees of prejunctional effect as shown by different degrees of train-of-four (TOF) fade.[2] In this study we have compared the neuromuscular blocking and prejunctional effects of cisatracurium with other neuromuscular blocking agents.

Ninety adult patients were included in the study with their informed consent but four of these were subsequently excluded because of protocol violations. They were anaesthetized with fentanyl 1–5 μg kg^{-1} and propofol 1.5–2.5 mg kg^{-1}, 66% nitrous oxide in oxygen and a propofol infusion. The ulnar nerve was stimulated at the wrist with supramaximal stimuli of 0.2 ms duration, in a TOF mode at 2 Hz every 12 s and the force of contraction of the adductor pollicis muscle recorded. Patients were allocated randomly to receive cisatracurium 0.05 or 0.1 mg kg^{-1} (Cis 0.05 and Cis 0.1), atracurium 0.5 mg kg^{-1} (Atra), mivacurium 0.15 mg kg^{-1} (Miv), vecuronium 0.08 mg kg^{-1} (Vec) or rocuronium 0.6 mg kg^{-1} (Roc), these being the approximate of one and two×ED$_{95}$ of cisatracurium and two×ED$_{95}$ of other blocking agents. The times to onset and various end-points of spontaneously occurring recovery were recorded. The TOF ratios at approximate heights of T1 of 90, 75, 50 and 25% during onset and recovery of block were calculated. The data were subjected to Kruskal-Wallis and Dunn tests.

Onset of maximum block was slower with both doses of cisatracurium compared with other blocking agents (see table 7). The recovery of block to all the end-points was significantly more rapid after mivacurium. The duration of action of cisatracurium 0.1 mg kg^{-1} was longer compared with equipotent doses of other blocking agents but the differences were not significant in this respect. Significantly greater fade in the TOF was observed with the lower compared with the higher dose of cisatracurium. Otherwise the differences in TOF ratios at various heights of T1 were small. Greater fade was observed during recovery than during the onset of block with all blocking agents Our results showed only small differences in the TOF fade between the equipotent doses of the relaxants.

Acknowledgment

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Key words
Neuromuscular block, atracurium. Neuromuscular block, cisatracurium. Neuromuscular block, mivacurium. Neuromuscular block, rocuronium. Neuromuscular block, vecuronium. Measurement techniques, neuromuscular block, train-of-four fade. Pharmacodynamics.

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Cardiovascular effects and time-course of action of cisatracurium in infants and children during thiopentone–alfentanil–nitrous oxide–oxygen anaesthesia

O. A. MERETOJA*, G. MEAKIN, T. TAIVAINEN*, R. J. PERKINS*, K. WIRTAVUORI*, A. K. MURPHY* AND L. RAIHA*
Departments of Anaesthesiology, Children's Hospital University of Helsinki, FIN-00290 Helsinki, Finland, and Royal Manchester Children's Hospital, Manchester

Cisatracurium (Nimbex) is a purified form of one of the stereoisomers of atracurium, which lacks significant histamine releasing properties in children and adults.[1 2] It has not been studied in

Table 7 Onset and duration of block and TOF ratios during onset of block (median and range). $^{a}n=13$, $^{b}n=14$, $^{c}n=8$, $^{d}n=11$, $^{e}n=10$, $^{f}n=2$, $^{g}n=12$, $^{h}n=9$, $^{i}n=6$; $^{*}P<0.05$ *vs* all except Cis 0.1; $^{**}P<0.05$ *vs* Cis 0.1; $^{+}P<0.05$ *vs* all except Cis 0.05

			Time (min) to		TOF ratios (%) at		
	n	Onset (min)	25% T1	TOF 0.8	T1 75%	T1 50%	T1 25%
Cis 0.05	14	4.8 (3.0–7.5)*	21.4 (11.8–28.7)	42.5 (33.2–47.4)	80 (73–85)	70 (56–84)**	56 (37–67)**
Cis 0.1	14	3.4 (2.1–5.6)	40.5 (20.6–50.0)^{a}	65.0 (39.6–77.7)^{a}	84 (76–89)	77 (67–81)	69 (55–76)
Atra	15	1.5 (1.2–2.3)**	42.7 (37.0–53.7)^{b}	68.9 (58.0–79.4)^{b}	81 (71–90)^{c}	74 (62–79)^{g}	63 (50–73)
Miv	15	2.1 (1.2–2.6)	15.1 (10.8–19.8)$^{+}$	24.5 (19.0–29.7)$^{+}$	82 (75–85)^{d}	74 (69–77)^{g}	64 (56–69)
Vec	13	2.0 (1.5–2.7)	30.5 (23.0–46.4)	60.2 (45.4–116.9)	82 (77–90)^{e}	74 (66–79)^{d}	65 (62–74)
Roc	15	1.0 (0.7–1.3)**	32.7 (18.1–57.3)	50.4 (28.4–76.1)	76 (73–79)^{f}	73 (64–74)^{h**}	63 (36–68)^{i**}

Table 8 Mean (SD) onset and recovery times of cisatracurium 0.15 mg kg^{-1} in infants and children

	Infants (1–23 mths)	Children (2–12 years)	*P*
Time in min to			
90% block	1.5 (0.6)	2.1 (0.3)	<0.001
Maximal block	2.0 (0.7)	3.0 (1.2)	<0.001
25% recovery	43.3 (6.2)	36.0 (5.4)	<0.001
95% recovery	64.8 (7.9)	55.0 (7.0)	<0.001
25–75% recovery time	11.7 (2.7)	11.1 (2.1)	NS

infants. Accordingly, we evaluated the cardiovascular effects and time-course of action of cisatracurium in infants compared with children.

Twenty-four infants (1–23 months) and 24 children (2–12 years) of ASA class I–II were studied. Premedication consisted of oral or nasal midazolam; anaesthesia was induced and maintained with thiopentone–alfentanil–nitrous oxide–oxygen. Routine monitoring consisted of ECG, non-invasive blood pressure and oxygen saturation. Neuromuscular transmission was monitored using single-twitch stimulation at 10-s intervals (Datex Relaxograph). After stable anaesthesia and calibration of the monitor, cisatracurium 0.15 mg kg^{-1} (3×ED$_{95}$) was administered as a rapid i.v. bolus. Onset and recovery data were analysed by the unpaired *t* test.

Cisatracurium 0.15 mg kg^{-1} produced no significant cardiovascular effects, cutaneous flushing or other untoward reactions. The onset and recovery times are shown in table 8.

Onset times were shorter and recovery times longer in infants compared with children; however, the differences were small and unlikely to be clinically important. We concluded that cisataracurium is a promising alternative to atracurium in paediatric anaesthesia.

Key words
Anaesthesia, paediatric. Neuromuscular block, cisatracurium.

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Effect of neuromuscular block using vecuronium on oxygen consumption in critically ill adults

P. B. Loan*, M. J. Symington*, R. K. Mirakhur[1], J. R. Johnston, T. J. Trinder* and C. J. Patterson[2]*
Department of Anaesthetics, Royal Victoria Hospital Belfast;
[1]Department of Anaesthetics, Queen's University Belfast;
[2]Department of Epidemiology and Public Health, Queen's University, Belfast

Neuromuscular blocking agents are often used to reduce oxygen consumption ($\dot{V}_{O_2}$-I) in intensive care patients.[1] A previous study showed a beneficial effect, particularly in patients who were moving before paralysis.[2] However, pancuronium, which has significant haemodynamic effects, was used in this study. Also, the one-directional crossover design used cannot detect carryover effects, or distinguish between treatment and period effects. This study was designed to examine any carryover, period or treatment effects of neuromuscular block with vecuronium on oxygen use in sedated critically ill intensive care patients.

Twelve patients were included in the study. All met criteria for the systemic inflammatory response and acute respiratory distress syndromes, and had had pulmonary arterial catheters in place for at least 12 h. Patients were excluded if neuromuscular block was indicated other than for ventilation. Sedation to Ramsay scale grade 5–6 was with morphine (or alfentanil if renal failure was present) and propofol infusions. Ventilation, and sedative, analgesic and cardioactive drug infusions were stable for at least 1 h before the study. Gastric tonometers were in place, and an i.v. infusion of ranitidine 50 mg 4-hourly was administered during the study.

Six patients each were allocated randomly to be paralysed first (PNN) or non-paralysed first (NPP) groups. Group PNN received vecuronium 0.05 mg kg^{-1} followed by an infusion to maintain one to two responses in the train-of-four (TOF). After 40 min, haemodynamic measurements and measurements of arterial and mixed venous oxygen saturations and partial pressures were made, in addition to gastric tonometric pCO$_2$. vO$_2$-I, oxygen delivery (DO$_2$-I) and gastric mucosal pH (pHi) were calculated by standard formulae. Neuromuscular function was allowed to recover spontaneously (TOF ratio >0.9) before two further 40-min periods, without blocking agent. Group NPP underwent three similar 40-min study periods, but in the order non-paralysed, paralysed, paralysed. The data were tested for period and carryover effects before assessing treatment effect using analysis of variance. $P<0.05$ was considered significant.

No carryover or period effects were observed. Vecuronium paralysis had no significant effect on the measured or calculated variables, including DO$_2$-I and vO$_2$-I (table 9). The results suggested no beneficial effect of neuromuscular block on DO$_2$-I, VO$_2$-I and pHi in non-shivering, sedated, critically ill patients.

Key words
Neuromuscular blocking agents, vecuronium. Oxygen, delivery. Oxygen, consumption. Critical care

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Functional iron deficiency in orthotopic liver transplantation

A. Davey-Quinn* and M. C. Bellamy
Intensive Care Unit, St. James's University Hospital, Leeds LS9 7TF

Functional iron deficiency (FID) has been described in renal failure, nutritional deficiency, and chronic ill health. An approach to assessment of FID has been proposed by MacDougal.[1] We have used this to quantify FID in patients presenting for liver transplantation, in an attempt to assess its consequences on outcome.

Forty-four consecutive patients undergoing liver transplantation during a 6-month period were studied. We measured preoperative ferritin concentrations, haemoglobin, and FID (proportion of hypochromic red blood cells measured by flow cytometry). Outcome variables included duration of hospital stay, intra-operative blood transfusion, and postoperative day 7, 14 and 21 haemoglobin and FID. Results, expressed as median (range), were analysed by Friedman ANOVA, Mann–Whitney *U* test, and multiple regression analysis.

Median preoperative haemoglobin was 11.0 (8.4–13.9) g dl^{-1}.

Table 9 Main oxygen use parameters with (P) and without (N) paralysis. DO2- I, VO2-I (ml min^{-1} m^{-2}) and pHi. (Mean [SD])

	Group NPP			Group PNN		
	N	P	P	P	N	N
DO2-I	752 (246)	772 (241)	748 (236)	730 (242)	739 (301)	705 (214)
VO2-I	228 (90)	230 (77)	220 (80)	207 (67)	203 (75)	194 (56)
pHi	7.37 (0.13)	7.39 (0.11)	7.42 (0.11)	7.28 (0.15)	7.25 (0.14)	7.26 (0.23)

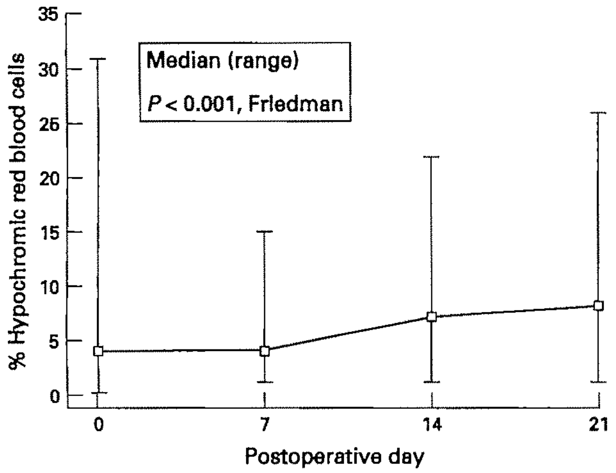

Figure 9 FID trend with time.

Seven patients (16%, 5–27%, 95%CI) had severe FID (>15% hypochromic RBC). Median preoperative hypochromic RBC count was 4 (0–31)%. After operation, this rose to a peak 8 (1–26)% at day 21 (P<0.001) (fig. 9). Median operative blood transfusion was 8 (0–21) units. Preoperative haemoglobin was lower in patients with FID, but this failed to reach statistical significance [10.4 (8.6–12) *vs* 11.1 (8.4–13.9) g dl^{-1}]. Likewise serum ferritin was lower but not significantly so in patients with severe FID [49 (14–1057) *vs* 132 (22–580) ng ml^{-1}], P=ns. Preoperative haemoglobin correlated with intra-operative blood transfusion. Independent predictors of hospital stay were age, FID and preoperative haemoglobin (P=0.05, r=0.44).

Functional iron deficiency is seen in patients presenting for orthotopic liver transplantation. FID could not be detected on the basis of haemoglobin or serum ferritin. Severity of FID correlated with duration of hospital stay. Further work is required to assess the effect of preoperative FID correction on outcome.

Key words
Liver, transplantation. Complications, functional iron deficiency.

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Is there a difference in myofilament calcium sensitivity between malignant hyperthermia susceptible and normal skeletal muscle?

S. M. Enright, F. R. Ellis, **P. J. Halsall*** and P. M. Hopkins
Academic Unit of Anaesthesia, St James's University Hospital, Leeds

Differences in response to triggering agents in malignant hyperthermia susceptible (MHS) and normal (MHN) skeletal muscle may be caused by different calcium sensitivities of the contractile apparatus. We wished to compare myofilament calcium sensitivities in MHS and normal, type I and II fibres.

We studied chemically skinned[1] single muscle fibres from six MHS and six MHN patients. Only fibres which generated a maximal tension of ≥80 mg were included. A total of 44 fibres were studied, 18 MHS and 26 MHN. Calcium sensitivity for each fibre was determined by observing isometric tension developed with increasing calcium concentrations (1×10^{-4} mmol litre^{-1} to 1.58×10^{-2} mmol litre^{-1}). Each fibre was then typed using strontium-induced tension[2] into either type I (slow twitch, oxidative) or type II (fast twitch, glycolytic). Dose-response curves for calcium concentration and isometric tension were constructed for the four groups of fibre. From these the calcium threshold concentration associated with half-maximal tension (pCa$_{50}$) and Hill coefficient were derived (table 10).

Table 10 Calcium threshold concentration (mean and 95% CI) associated with half-maximal tension (pCa$_{50}$) and the Hill coefficients for calcium-induced tension in type I and type II single chemically skinned muscle fibres from MHS and MHN individuals

Fibre type	Mean pCa$_{50}$	95% CI	Hill coefficient
MHN I	6.06	6.05–6.07	5.09
MHN II	5.98	5.80–6.01	4.35
MHS I	6.06	5.99–6.12	5.02
MHS II	5.98	5.90–6.03	4.16

We have shown a difference in calcium sensitivity between type I and type II MHN muscle fibres as previously described.[3] We have shown no difference in calcium sensitivity between MHS and MHN muscle. We have found no evidence to suggest that increased calcium sensitivity of the contractile apparatus contributes to the syndrome of MH.

Key words
Hyperthermia. Muscles, skinned fibres. Ions, calcium.

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Does the insertion of earplugs affect the bispectral index of the sedated patient in the intensive care unit?

A. J. Pearson, C. J. D. Pomfrett and B. J. Pollard
University Department of Anaesthesia, Manchester Royal Infirmary, Manchester

The bispectral index (BIS) of sedated intensive care unit (ICU) patients has previously been shown to increase during nursing intervention and physiotherapy.[1] Whether this is because of arousal resulting from mechanical stimulation or the effect of noise levels is unclear. Recent work has shown that noise levels in the ICU and in operating rooms consistently remain above 60dB(A), which is classed as the "wake-up" threshold in humans.[2]

ICU sedation aims to provide analgesia, anxiolysis and amnesia in patients, and as such may aid sleep. However in the presence of noise greater than 60dB(A), many sedated patients might find it difficult to sleep. We hypothesized that the combination of ICU sedation and the use of earplugs to reduce the arousal caused by noise might be valuable. This study sought to investigate if the insertion of earplugs into the ears of sedated ICU patients caused any alteration in BIS consistent with more effective sedation and reduced levels of consciousness.

Twelve ICU patients were studied. All patients were receiving fentanyl and midazolam by continuous infusion according to unit policy. BIS was recorded using the Aspect A1000 monitor with "zipprep" electrodes placed in a frontal/mastoid montage. Recordings were made at 5-s intervals and logged directly onto a laptop computer. BIS was recorded on each patient for 1 h. During this hour, patients had either no earplugs in for the first 30 min and earplugs in for the second 30 min or *vice versa*, the order being selected randomly by the toss of a coin. Sound levels were monitored during recording using a simple sound meter. The data were subsequently transferred to a desk top computer and converted into a Microsoft Excel spreadsheet for analysis

In most cases the results did not follow the expected pattern. One patient did demonstrate a significant decrease in BIS after the insertion of the earplugs (P<0.001 Student's t test). Conversely one patient demonstrated a significant increase in BIS after the insertion of earplugs (P< 0.001). Individual data from the other 10 patients were varied with four patients exhibiting a higher overall mean in the earplug group. Overall the data showed no significant difference between the group means (P= 0.28), and there were no significant differences in variance between the groups (P=0.59 ANOVA). Sound levels monitored during EEG recording periods were found to be consistently between 55-70dB(A) with peak increases up to 90-95dB(A) caused by alarms and the telephone ringing.

In this group of patients there was no evidence to suggest that earplugs might reduce the arousal caused by noise in ICU.

Acknowledgement

We acknowledge the support of Aspect/SpaceLabs Medical for providing the Aspect A1000.

Key words
Intensive care. Measurement techniques, electroencephalogram.

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Intravenous magnesium does not modify ischaemia–reperfusion syndrome in orthotopic liver transplantation

R. Srinivasa*, A. Morris*, S. M. Enright and M. C. Bellamy
Intensive Care Unit, St James's University Hospital, Leeds LS9 7TF

During human orthotopic liver transplantation (OLT), graft reperfusion may be accompanied by ischaemia–reperfusion syndrome, potentially leading to poor graft function and death. These changes are thought to be mediated in part by changes in cytosolic calcium. Magnesium is a physiological calcium antagonist, and has been used to attenuate ischaemia–reperfusion in cardiac surgery[1] and other models. Animal work suggests protection from hepatic ischaemia–reperfusion injury.[2] We have therefore assessed its effects in OLT.

In a prospective randomized double-blind trial, 40 patients undergoing elective liver transplantation were randomized to receive $MgS0_4$ 10 mmol or placebo during the anhepatic phase at discontinuation of portal bypass (10 min before graft reperfusion). All patients received a standard anaesthetic (alfentanil–air–oxygen–desflurane) and underwent venovenous bypass. Intracellular calcium in monocytes, postoperative liver function tests on days 1, 3 and 5, and mortality were evaluated. Results are given as median (interquartile range). Groups were compared using Mann–Whitney *U* test, and correlations explored by multiple regression.

No patient died during the study. Patient charecteristics in the groups were similar. No variable differed significantly between groups.

As previously described, monocyte intracellular calcium increased after reperfusion in both groups ($P<0.003$). There was no correlation between ischaemic time and outcome. Post-reperfusion $Ca^{2+}i$ correlated with pre-reperfusion $Ca^{2+}i$ ($r=0.9$, $P<0.001$). Both pre- and post-reperfusion $Ca^{2+}i$ correlated with day 3 ALT ($r=0.44$, $P<0.01$ and $r=0.48$, $P<0.005$) but not with promthrombin time or bilirubin (table 11).

Magnesium treatment at this dose did not modify the ischaemia–reperfusion syndrome. Intracellular calcium increased after liver graft reperfusion. Graft function after operation may reflect recipient leucocyte cytosolic calcium.

Key words
Complications, reperfusion syndrome. Ions, magnesium.

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Table 11 Magnesium treatment does not modify ischaemia–reperfusion syndrome

Variable	Placebo group	Magnesium group
Cold ischaemic time	625 (530–710) mins	685 (573–805) min
Pre-treatment Ca^{2+}_i	13.9 (6.7–21.5) nmol litre^{-1}	17.2 (9.0–48.8) nmol litre^{-1}
Post-reperfusion Ca^{2+}_i	19.8 (12.4–30) nmol litre^{-1}	22.6 (12.4–44) nmol litre^{-1}
ALT day 1	562 (253–1216) iu litre^{-1}	411 (146–895) iu litre^{-1}
ALT day 3	329 (130–719) iu litre^{-1}	277 (145–670) iu litre^{-1}
ALT day 7	131 (65–288) iu litre^{-1}	133 (75–254) iu litre^{-1}
PT day 1	21 (20–27) s	19 (18–22) s
PT day 3	19 (16–24) s	19 (16–24) s
Bilirubin day 3	66 (30–131) mmol litre^{-1}	58 (46–118) mmol litre^{-1}
Bilirubin day 7	56 (45–155) mmol litre^{-1}	60 (32–94) mmol litre^{-1}

POSTER PRESENTATIONS

Synergistic effect of fentanyl and midazolam on phrenic nerve activity in rabbits

D. Ma*, S. M. Sapsed-Byrne*, M. K. Chakrabarti and J. G. Whitwam
Department of Anaesthesia, Royal Postgraduate Medical School, Hammersmith Hospital, Du Cane Road, W12 0NN London

A combination of fentanyl and midazolam is often used clinically[1] and while Ben-Shlomo and colleagues reported that midazolam has a synergistic effect with fentanyl on consciousness,[2] as yet the nature of their interaction on ventilation is unknown. This study examined the combined effect of midazolam and fentanyl on phrenic nerve activity (PNA) in rabbits.

Seventeen New Zealand White rabbits were anaesthetized (methohexitone bolus 10–15 mg kg^{-1} and 1% α-chloralose 15–20 mg kg^{-1} i.v.), paralysed (suxamethonium 10 mg i.v. every 20–30 min) and artificially ventilated. pHa, blood-gas tensions and oesophageal temperature were maintained within the normal ranges. The phrenic nerve was exposed in the neck, dissected, desheathed and cut distally, and mounted on electrodes in a mineral oil pool for recording efferent activity. The rabbits were

Table 12 $ED_{25,50,75}$ (95% confidence intervals) for fentanyl (μg kg^{-1} i.v.), midazolam (mg kg^{-1} i.v.) and their interactions on phrenic nerve activity and the ratios of predicted/observed (P/O) $ED_{25,50,75}$ for fentanyl. Predicted doses were calculated from the dose-response curve of fentanyl if the interaction of the two drugs was additive

			Midazolam (0.05 mg kg^{-1} i.v.)+fentanyl		
	Fentanyl	Midazolam	Predicted	Observed	P/O
ED_{25}	1.5 (1.1–1.9)	0.08 (0.04–0.12)	0.9	0.4 (0.3–0.6)	2.3
ED_{50}	3.9 (3.2–4.7)	0.4 (0.3–0.5)	2.4	1.2 (0.5–1.4)	2
ED_{75}	10.1 (8.9–12.6)	2.2 (1.7–3.3)	6.0	3.1 (2.6–3.6)	1.9

divided randomly into three groups. Group 1 ($n=5$), fentanyl was administered in incremental doses of 1, 1, 2, 4 and 8 μg kg^{-1} i.v., each dose over 20 s at 5-min intervals until PNA was abolished. Group II ($n=7$), midazolam was administered in incremental doses of 0.05, 0.05, 0.1, 0.2, 0.4, 0.8, 1.6 and 3.2 mg kg^{-1} i.v., each dose over 20 s at 5-min intervals until maximum depression of phrenic nerve activity was obtained. Group III ($n=5$), a single dose of midazolam 0.05 mg kg^{-1} i.v. was administered, followed 5 min later by fentanyl in incremental doses of 0.5, 0.5, 1, 2 and 4 μg kg^{-1} i.v until the abolition of phrenic nerve activity. At the end of the experiment, it was found that 0.5 mg naloxone and 0.2 mg flumazenil (i.v.) were required to reverse the effect of fentanyl and midazolam respectively.

$ED_{25,50,75}$ (95% confidence intervals) calculated from the dose-response curves are presented in table 12 which demonstrates that the combined effects of midazolam and fentanyl on phrenic nerve activity is synergistic.

These results showed synergistic interaction between the depressant effect of midazolam and fentanyl on phrenic nerve activity and hence potentially on ventilation.

Key words
Phrenic nerve activity. Analgesics, fentanyl. Hypnotics, benzodiazepines, midazolam. Rabbit.

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I.v. regional anaesthesia. Comparison of 0.25% prilocaine with or without 5% dextrose

A. Makin[2]*, M. Basler[1]*, M. Serpell[1], S. Kennedy[2]*, P. Bolton[2]* and D. Carson[2]*
Directorate of Anaesthesia, [1]Western Hospitals NHS University Trust, Glasgow, G11 6NT, and [2]Ninewells Hospital and Medical School, Dundee, DD1 9SY

The presence of glucose helps to maintain normal neural conduction.[1] Glucose is usually lacking in solutions used for nerve conduction block except for subarachnoid anaesthesia where its use has been shown to shorten the onset and duration of block.[2] Our aim was to characterize its effects on i.v. regional anaesthesia (IVRA).

Six healthy, fasted male volunteers aged 25–55 years were recruited. Each subject underwent IVRA of the non-dominant arm on two occasions separated by at least two weeks. A 23-gauge cannula was inserted into the dorsum of the hand for the administration of the local anaesthetic. The limb was exsanguinated using an Esmarch bandage and a padded pneumatic tourniquet was inflated to 250 mm Hg. After removal of the bandage, baseline maximum muscle power was measured by the subject squeezing a 1000 ml infusion bag connected to a pressure transducer. Forty ml of local anaesthetic was injected into the arm over 1 min. The solution consisted of 0.25% prilocaine in normal saline or 5% dextrose solution at room temperature. The subject received one solution on the first occasion and the other on the second in a double-blind and randomized fashion. After completion of injection, sensation and motor power were tested at 1-min intervals Sensation was tested over six sites of the forearm in random order, being reported as sharp, touch or absent. At 10 and 20 min the amount of forearm pain was indicated on a visual analogue scale (VAS). Twenty minutes after injection the tourniquet was deflated and testing continued until modalities returned to normal. Monitoring included pulse oximetry and non-invasive blood pressure. Statistical analysis included Student's paired *t* test and one-sample Wilcoxin signed-rank test

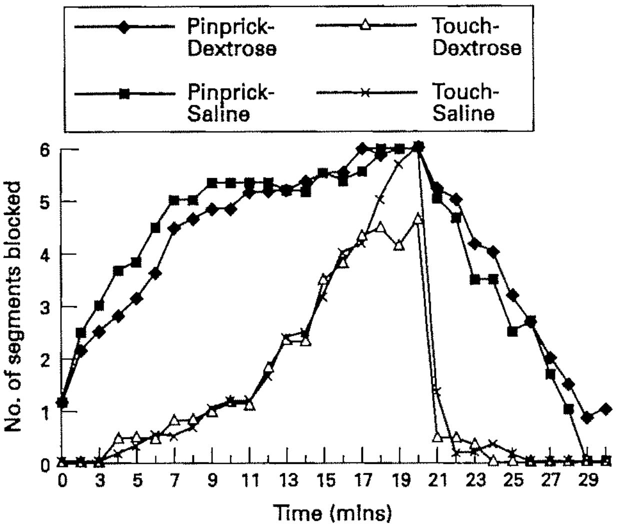

Figure 10 Time *vs* number of segments blocked.

There was no difference in onset or regression of block, or forearm pain scores between the groups. Loss of sharp sensation preceded touch which preceded motor block (fig. 10).

Glucose did not affect nerve conduction during IVRA. This may be because the concentration of prilocaine was too potent or the glucose concentrations achieved at the nerve fibres were inadequate because of redistribution or metabolism.

Key words
Anaesthesia, regional. Anaesthetic techniques, regional, i.v.

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CORRESPONDENCE

Thorascopic sympathectomy

Sir,—I read with interest the review article by Fredman, Olsfanger and Jedeikin on thorascopic sympathectomy in the treatment of palmer hyperhidrosis.[1] The authors reported on the cardiac complications and noted the two reported cases of intraoperative cardiac arrest,[2] the postulated pathophysiology being that pre-excitation of the myocardium by sympathetic ablation lowers the threshold for ventricular fibrillation.

I wish to report on a 31-yr-old woman undergoing left-sided thorascopic sympathectomy. Induction of anaesthesia was uneventful and a left-sided 37Ch Mallinckroft double-lumen tube was inserted without difficulty. Monitoring included electrocardiogram (ECG) with lead 2 selected, non-invasive arterial pressure (AP), pulse oximetry (Sp_{O_2}), and inspiratory and expiratory gas concentrations. The left lung was collapsed and deflated by clamping the endobronchial tube and opening to air. A size 12 mm trocar was introduced into the chest between the third and fourth ribs in the mid-axillary line under direct vision and carbon dioxide 2 litre insufflated with a pressure limit of 5 mm Hg. Although the lung was deflated, it was difficult to see the T4 ganglia and therefore additional carbon dioxide was insufflated, with the same pressure limit. At this point the patient developed sudden onset of ST segment depression on the ECG. This was not accompanied by changes in P or R waves suggesting that this was not solely the result of a change in the cardiac axis as a result of tension pneumothorax. Arterial pressure decreased from 90/60 to 60/40 mm Hg, with no significant change in heart rate. The surgeon was informed of these changes, and immediate release of carbon dioxide from the hemi-thorax resulted in restoration of a normal ECG within 30 s, and a normal AP after 1 min without the use of vasopressors. As she was now cardiovascularly stable the T2–4 ganglia and sympathetic chain were diathermied. At no time did Sp_{O_2} decrease to less than 96%. The left lung was subsequently fully reinflated and no chest drain was required. Her recovery was uneventful and she was discharged home the next day.

As mentioned in the review, acute hypotension is a recognized complication of capnothorax.[3] In this case, hypotension followed ischaemic changes suggesting that hypotension was attributable, at least in part, to acute reversible myocardial ischaemia. The two reported cases of cardiac arrest occurred during left-sided procedures. It is possible that excess pressure, especially during left-sided procedures, leads to myocardial ischaemia and hence to arrhythmias. Possible mechanisms include: coronary vessel compression as the myocardium is traversed; coronary vessel spasm; reduced coronary flow as a result of torsion of the mediastinum; and reduced coronary flow caused by hypotension. In this case it seems unlikely that hypotension alone was the cause of ischaemic changes as an arterial pressure of 60/40 mm Hg in a healthy, young patient would not usually be expected to be accompanied by ST segment depression. This makes a direct pressure effect seem more likely. Limits on the volume of carbon dioxide were suggested as 1.2 litre,[4] 2.0 litre[5] and 1.0 litre in the review. This case further illustrates the need for extreme caution in the volume and rate of insufflation, but also that myocardial ischaemia, as evident on the ECG, may be the cause of an arrhythmia rather than a lowered threshold for ventricular fibrillation caused by sympathetic ablation.

A. J. D. Parry-Jones
Magill Department of Anaesthesia
Chelsea and Westminster Hospital
London

1. Fredman B, Olsfanger D, Jedeikin R. Thorascopic sympathectomy in the treatment of palmer hyperhidrosis: anaesthetic implications. *British Journal of Anaesthesia* 1997; 79: 113–119.
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Sir,—Dr Parry-Jones described a case of acute ST segment depression associated with excessive pneumothorax during thorascopic sympathectomy. Unfortunately, because of the lack of detail of the surgical technique and anaesthetic monitoring, full and accurate analysis of the case presentation is difficult.

In our opinion the pathophysiological events leading to ST depression described in this case were attributable primarily to the inadvertent tension pneumothorax. First, excessive intra-thoracic pressure decreases venous return, stroke volume, cardiac output, aortic root pressure and coronary perfusion pressure. Second, unilateral tension pneumothorax shifts the mediastinum and may result in kinking of the bronchi to the ventilated lung. These events result in hypoxaemia and a decrease in myocardial oxygen supply and may cause acute myocardial ischaemia. Our hypothesis is supported by the fact that all pathological findings disappeared rapidly after the release of the tension pneumothorax. Therefore, we disagree with the conclusion that "hypotension was attributable, at least in part, to acute reversible myocardial ischaemia". As non-invasive arterial pressure monitoring has the disadvantage of being time-cycle dependent, it is possible that arterial pressure during the acute event was much lower than actually captured and displayed. Thus one cannot state that "an arterial pressure of 60/40 mm Hg in a healthy, young patient would not usually be expected to be accompanied by ST segment depression."

When providing anaesthesia for thorascopic sympathectomy the advantages and potential pitfalls of the various techniques should be remembered.[1] When using a tracheal tube, surgical exposure is dependent on continuous insufflation of carbon dioxide into the intrapleural space.[2] To avoid inadvertent tension pneumothorax a pressure-limited, variable flow insufflator is used. In contrast, when using the endobronchial technique, carbon dioxide insufflation is performed to augment lung collapse and protect the lung during insertion of the endoscopic instruments. Thereafter, collapse of the entire lung is accomplished and maintained by the endobronchial tube and carbon dioxide insufflation plays no part in providing surgical exposure. As a result, a pressure-limited, variable flow insufflator is not necessarily required. Thus with the endobronchial technique a tension pneumothorax may occur and extreme caution should be exercised if additional gas is insufflated after lung collapse. Finally, irrespective of the technique used, hypoxaemia is a major concern during thorascopic sympathectomy. It is for this reason that we recommend vigilant Sp_{O_2} monitoring during lung collapse.[3]

B. Fredman
D. Olsfanger
R. Jedeikin
Department of Anesthesiology and Critical Care
Meir Hospital
Kfar Sava, Israel

1. Fredman B, Olsfanger D, Jedeikin R. Thorascopic sympathectomy in the treatment of palmer hyperhidrosis: anaesthetic implications. *British Journal of Anaesthesia* 1997; 79: 113–119.
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Simulated anaesthetic emergencies

Sir,—We congratulate Drs Byrne and Jones for their study of an anaesthesia simulator as a tool for performance evaluation.[1] We have operated a realistic simulation centre for several years[2] and have been involved extensively in the research of anaesthesia simulation as a potential assessment tool.[3 4] We would like to offer the following comments.

The purchase of a realistic simulator represents only a fraction of the cost for the construction of a simulation centre. In fact, the operating costs (mostly salaries for staff) outgrow this initial capital cost within 2 yr.[5] Trying to save money by advocating the initial purchase of a less realistic simulation system may therefore confer only a short-lived benefit and limit the option of expanding simulation of realistic environments in the long term. Furthermore, simplified part-trainers appear to offer a less valuable learning experience compared with realistic simulation environments.[6] In order to substantiate claims that subjects use the same mental models as in real life it is necessary to present data to document that participants indeed "suspend disbelieve" (e.g. rating scales on realism). Otherwise the correlation of findings to clinical events remains speculative.

Physician assessment in anaesthesia to date remains largely a subjective process. Availability of simulators offers the opportunity to expose different individuals to identical scenarios in a high fidelity environment and compare their performance to a "gold standard" reference group. The development of a new assessment tool, however, requires careful evaluation of its reliability and validity[7] in order to define its value compared with accepted evaluation tools.

Drs Byrne and Jones did not measure the reliability of their proposed evaluation tool and given that they did not define the final end-point of a successful intervention, inter-rater reliability may indeed be poor. They neither defined nor validated their time definitions (e.g. the "gold standard" time until the "gold standard" intervention) and did not provide measurements of a reference group (e.g. additional reference group of certified anaesthetists).

It is of interest that the responses to their simulated emergencies appeared to yield such variable results (e.g. some items such as awareness had consistently good responses whereas others such as asystole had mostly poor responses). Statistical tests to measure internal consistency are available (e.g. Crohnbach's alpha) and are helpful in designing tests with internally consistent items. The clinical implications of untreated awareness are very different from untreated asystole and the different responses could be a result of varying degrees of perceived difficulty. In that case, individual scores should be weighted accordingly when combined into the final score for statistical analysis

We believe that simulation has the potential to address some of the shortcomings of traditional evaluation tools. However, practical and clinically relevant scoring systems need to be developed and the reliability of these scoring systems demonstrated. A data base of performance measures of various clinical groups (e.g. the "gold standard" *vs* trainees of various experience) should be generated and demonstrate feasibility and validity of the evaluation tool. Until these studies[8] are complete it is premature to declare that "simulators can be used to assess the ability of anaesthetists to deal with anaesthetic emergencies".

M. KURREK
J. H. DEVITT
Canadian Simulation Centre for Human Performance and Crisis Management Training
Sunnybrook Health Science Centre
Department of Anaesthesia
University of Toronto
Ontario, Canada

1. Byrne AJ, Jones JG. Responses to simulated anaesthetic emergencies by anaesthetists with different durations of clinical experience. *British Journal of Anaesthesia* 1997; 78: 553–556.
2. Kurrek MM, Fish KJ. Anaesthesia crisis resource management training: An intimidating concept, a rewarding experience. *Canadian Journal of Anaesthesia* 1996; 43: 430–434.
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Sir,—We applaud Drs Byrne and Jones for their study[1] of the performance of anaesthetists at different levels of experience in the management of low-fidelity simulations of critical events. The authors have detected the same characteristics of anaesthetists' technical responses as were found over the past 8 yr in previous studies using both hands-on simulators[2–4] and computer-screen simulators.[5] These characteristics are: (i) significant variability in response between individuals and between events; (ii) modest improvement in performance caused by increased anaesthesia experience, especially compared with the most junior personnel; (iii) occurrence of serious, even catastrophic, errors at every level of experience; and (iv) lack of uniform adherence to published guidelines for managing critical events.

These characteristics appear to be reproducible features of anaesthetist performance. That they can be detected with instruments of different fidelity is not surprising (one can see craters on the moon with the naked eye and with a telescope). Furthermore, Byrne and Jones compared their results using the low-fidelity ACCESS simulator[6] with those obtained with early versions of our more hands-on simulator (CASE 1.2/1.3).[7] CASE 1.2/1.3 had greater fidelity than ACCESS because it provided monitoring data via actual clinical monitors, but compared with today's simulators and simulation environments, CASE 1.2/1.3 was itself a low-fidelity simulator.

There were several methodological problems in this study. The presence of the "tutor" acting as an assistant (while operating the simulator) could have altered the results, especially if the tutor was not blinded to the experience level of the subjects. Also, having a tutor to pass equipment is not routine in most anaesthetic environments. Actions were timed to the nearest 30 s, a rather coarse measure given the rapidity with which some diagnostic and therapeutic manoeuvres can be completed (some can even be conducted in parallel), as demonstrated in previous studies in which the simulations were videotaped.[3 4 8–10] Hypervigilance (expecting problems that are not present) and cavalier behaviour (not responding avidly because the patient is not a real human being) are common findings in simulation studies and can affect performance, but these issues were not mentioned by the authors.

We view with scepticism the contention of the authors that "to measure performance...it is not necessary to construct a 'high-fidelity' environment, but merely to provide enough realism to enable those tested to suspend disbelief". First, the authors have not proved that they accurately tested the true *performance* of their subjects, only that they identified characteristics of performance similar to those measured previously. Second, there is no proof that "...subjects used the same mental models as they use in real life and results are therefore valid." No systematic analysis of mental models was conducted. Third, while we agree that suspension of disbelief is necessary when a plastic manikin represents a human being, the authors provided only an anecdote suggesting that one subject suspended disbelief; they provided no data that subjects did so in general. Hence, if the goal was to determine the level of simulator fidelity required to support a given type of performance assessment, this study shed little light on the question. To do so it would be necessary to test the same individuals using comparable scenarios on simulators of differing fidelity.

Moreover, the type of performance assessed in this study, and in previous studies cited, is only a limited portion of clinical skill–technical performance. When simulations are conducted using realistic replications of a clinical environment, complete with actual equipment and supplies, and a full set of clinical personnel such as nurses, surgeons, anaesthetists and technicians, a more complete set of clinical skills can be probed. Over the past 7 yr many investigators have been examining more comprehensive aspects of performance, including crisis management behaviours such as leadership, communication and teamwork.[8 11 12] Techniques to measure these aspects of performance and technical management of complex situations are currently under development.[13–16] We believe that to address the full complexity of clinical management for research studies or for training it is necessary to probe clinicians in settings that challenge the full scope of their abilities. However, as for other part-task trainers and low-fidelity simulators, ACCESS may be useful for investigating and teaching restricted aspects of patient care.

Finally, many simulation centres have expanded their attention beyond anaesthesia to conduct research and training on comprehensive management issues in a variety of medical domains, including combined team performance in the operating room, delivery suite, emergency department and intensive care unit.[17] Such expansion is desirable not only to maximize the benefit of simulation-based training, but also as a way of sharing expenses between multiple user groups. To address the various different clinical arenas, high-fidelity, model-driven multipurpose patient simulators are essential tools in creating a simulation environment that replicates the true complexity of the clinical environment being targeted.

D. M. GABA
S. K. HOWARD
Anesthesiology Service,
VA Palo Alto HCS and
Department of Anesthesia
Stanford University School of Medicine
CA, USA

1. Byrne AJ, Jones JG. Responses to simulated anaesthetic emergencies by anaesthetists with different durations of clinical experience. *British Journal of Anaesthesia* 1997; **78**: 553–556.
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Sir,—We note the comments of Drs Kurrek and Devitt and Drs Gaba and Howard on our article.[1]

Unfortunately, there are some factual errors in the comments of Drs Kurrek and Devitt. First, they assert that it is "necessary to present data to document that participants indeed 'suspend disbelief' (e.g. rating scales about realism)". We have previously published such data.[2] Thus, when we asked subjects who had gained experience on our ACCESS simulator if they agreed with the statement, "The patients' responses were realistic" the median response was 8.5 on a scale of 0 to 10 (0=disagree, 10=agree). Consequently, the realism of the ACCESS simulator was comparable with that of any other anaesthesia simulator.

Second, their statement that the operating costs of a simulator outgrow the initial capital cost within 2 yr is only true for high-fidelity simulation centres. The ACCESS simulator has been designed to be operated by a single tutor and avoids the large operating costs they describe.[3] It can and is being used by single departments of anaesthesia with minimal running costs.

Third, they make the unjustified assertion that "simplified part-trainers appear to offer a less valuable learning experience compared with realistic simulation environments". The claim is refuted by one of their own abstracts. This described subjects' ratings of an unsupported session on a screen-based simulator (ASC) compared with involvement in two simulations on a full-scale simulator, followed by a review of their performance on videotape. As their own abstract states,[4] "The main criticism of the ASC program was the lack of feedback on performance which limited learning". Any educational tool will be rated poorly by subjects if it is used incorrectly.

Drs Gaba and Howard make great claims about complex simulators enabling "realistic replication of a clinical environment complete with .... a full set of clinical personnel such as nurses, surgeons, anaesthetists and technicians". Yet two paragraphs before this statement they objected to our having a "tutor" acting as an assistant because such a person "is not routine in most anaesthetic environments". While this may reflect the poor level of anaesthetic support in the USA, it is certainly not so in the UK where no anaesthetic can be given without the presence of a fully trained operating department assistant (ODA) whose role is to assist and pass equipment.

While the simplicity of the ACCESS system makes it easy to emphasize differences between training on a simple simulator and practising real life anaesthesia, there is no evidence that these differences reduce the educational value of the simulation. To date there have been no published articles on high-fidelity anaesthesia simulators which demon-strate an advantage for such an expensive approach. In fact, where comparisons have been made in aviation,[5] a $30 (£18) plywood mock-up was found to be as effective as a high-fidelity simulator and was no worse than training on a real aircraft. The cost of purchase and operation of a single high-fidelity simulation centre is likely to exceed that of 250 ACCESS simulators, with the latter having the capacity to train vastly larger numbers of anaesthetists. Many of the references quoted are small, limited studies describing equipment or evaluations published only in abstract form. We agree that it is vital to investigate the psychology of dealing with critical incidents and better define what we mean by performance. We also agree with their analogy of not needing high-resolution telescopes to see craters on the moon when simple, cheap glasses may be all that is needed.

A. J. Byrne
J. G. Jones
University Department of Anaesthesia
Addenbrooke's Hospital
Cambridge

1. Byrne AJ, Jones JG. Responses to simulated anaesthetic emergencies by anaesthetists with different durations of clinical experience. *British Journal of Anaesthesia* 1997; **78**: 553–556.
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Pigs are not humans

Sir,—It was with considerable interest that we read the article of Lentschener and co-workers on the haemodynamic repercussions of pneumoperitoneum in the pig.[1] Although we share the authors' caution concerning extrapolation of animal data to clinical experience in humans, several points in this study which contradict examples in the literature may have resulted in inappropriate conclusions.

Several studies on the haemodynamic effects of pneumoperitoneum have been carried out in the pig[2–4] and have given different results to those of Lentschener and colleagues, being similar to changes observed in humans.[5] Most of the studies quoted by Lentschener and colleagues were carried out in the dog[6 7] which, on the basis of the authors' conclusions on the differences between species, are equally difficult to extrapolate. Moreover, in humans, some studies have not always found the changes usually observed during pneumoperitoneum.[8 9]

Some factors may influence the haemodynamic repercussions of pneumoperitoneum. The most important would appear to be the the state of hydration of the patient; hypervolaemia limits the haemodynamic effects of peritoneal insufflation.[3 6] This could be the case in the study of Lentschener and colleagues where significant vascular filling was used (Ringer's lactate 500 ml h^{-1} for animals weighing approximately 18 kg). The high pulmonary capillary pressure and cardiac flow rate values agree with this hypothesis. Another factor which influences venous return during pneumoperitoneum is the position of the patient[2] and in this study it is not clear in what position the animals were placed. The type of anaesthesia can also have considerable influence on the haemodynamic repercussions observed during pneumoperitoneum[4 6] and it would be interesting to know the exact doses of fentanyl and ketamine used during this study. In addition, we are not sure that domestic pigs weighing 40 kg should be considered as adults.

Without wishing to cast doubt on the results, we feel that experimental and anaesthetic conditions can considerably influence the results of experimentation, which implies that the conclusions should be guarded, especially when they contradict those of most of the literature.

J. E. Bazin
P. Schoeffler
Department of Anaesthesia
University Hospital
Clermont-Ferrand, France

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Sir,—Thank you for the opportunity to reply to Drs Bazin and Schoeffler. We noted that Bazin and Schoeffler supported our conclusions that: (a) haemodynamic changes recorded when intraperitoneal pressure is increased differ depending on the study and (b) pharmacological or physical potentiating agents may alter haemodynamic changes associated with increased intraperitoneal pressure in humans and in animal models. However, in our opinion, the objections raised by Bazin and Schoeffler are not supported by the articles quoted in their reference list.

With the aim of supporting the fact that haemodynamic changes resulting from increased intraperitoneal pressure in humans may be reproduced reliably in pigs, Bazin and Schoeffler refer to two models (references 2 and 3 of the letter). Indeed, Ho and colleagues (reference 3 of the letter) maintained general anaesthesia throughout their study by continuous i.v. infusion of ketamine. Therefore, the increase in both arterial pressure and systemic vascular resistance may have been related to the direct sympathetic effect of i.v. ketamine.[1] Furthermore, in the investigation conducted by Junghans and colleagues (reference 2 of the letter), general anaesthesia was maintained throughout the study by nitrous oxide exclusively. Nitrous oxide is a weak analgesic which does not produce surgical analgesia. Therefore, pain may have accounted for the increase in arterial pressure. Moreover, in the study of Junghans and colleagues, arterial carbon dioxide tension increased from 4.5±0.1 to 6.4±0.1 kPa when pneumoperitoneum was created. This acute hypercapnia may also explain the increase in arterial pressure and systemic vascular resistance in this study. Finally, Bazin and Schoeffler are the only authors who reported, in an abstract (reference 4 of the letter), that they reliably reproduced haemodynamic changes in pigs resulting from increased intraperitoneal pressure in humans, with no potentiating agent. However, the method was not detailed sufficiently in the short abstract. Therefore, we do not understand how they could produce these haemodynamic changes in pigs when other investigators have failed to do so.

In our investigation, volume expansion may explain the high pulmonary capillary pressure measured in pigs. However, neither the study of Ho and colleagues nor that of Diamant, Benumof and Saidman (references 3 and 6 of the letter) demonstrated suppression of haemodynamic changes associated with increased intraperitoneal pressure by volume expansion in previously euvolaemic animals. Thus, Ho and colleagues studied the effect of pneumoperitoneum on haemodynamics in haemorrhaged pigs, which were compared with euvolaemic animals, with no reference to hypervolaemia. Furthermore, Diamant, Benumof and Saidman studied the effect of hypovolaemia on cardiac function after intraperitoneal pressure was increased to 40 mm Hg. This is higher than the 15 mm Hg of pressure used during laparoscopic surgery.

Bazin and Schoeffler questioned in which position haemodynamic data were recorded in our study. As described in the methods, haemodynamic data were recorded in the horizontal position.

We did not investigate pigs in other positions as we failed to reliably reproduce haemodynamic changes associated with pneumoperitoneum in the supine position.

Bazin and Schoeffler suggested that the way we conducted general anaesthesia may have altered our findings. First, general anaesthesia is induced in pigs with i.m. ketamine in most investigations. I.m. ketamine was used for induction of general anaesthesia in most studies mentioned in Bazin and Schoeffler's letter (references 1–4, 7, 8). Ketamine stimulates the sympathetic system and is likely to cause increases in arterial pressure and systemic vascular resistance.[1] As increases in arterial pressure and systemic vascular resistance were expected in our investigation but did not occur, we conclude that ketamine had no effect. The method of anaesthesia was discussed extensively in our article and in our opinion we definitively ruled out possible pharmacological contamination of our model.

C. Lentschener
D. Benhamou
Hôpial Antoine Béclère
Clamart, France

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Obstruction of the lumen of a plastic 15-mm connector inserted into a cut paediatric tube—Is it possible to avoid this damage?

Sir,—We read with interest the report of a critical incident by Gupta and Harry[1] illustrating the risks of inserting a connector after cutting a paediatric tube. This problem, encountered with Portex 8.5-mm paediatric tracheal tube connectors, was described originally by May and Kirton in 1993.[2]

At about the same time, we had a similar experience with a 3.5-mm internal diameter (id) tracheal tube (TT) produced by Rusch, Germany. Immediately before anaesthesia was induced in an 8-month-old boy with an incarcerated inguinal hernia, the 3.5-mm id TT had been cut to 12 cm. While trying to insert the plastic 15-mm connector into the proximal end of the cut tube, I noted that the connector buckled inwards, occluding its lumen. The damaged connector was removed and a fresh connector, originally packed with a 3.5-mm id TT, was inserted into the cut tube without damage. Anaesthesia was uneventful.

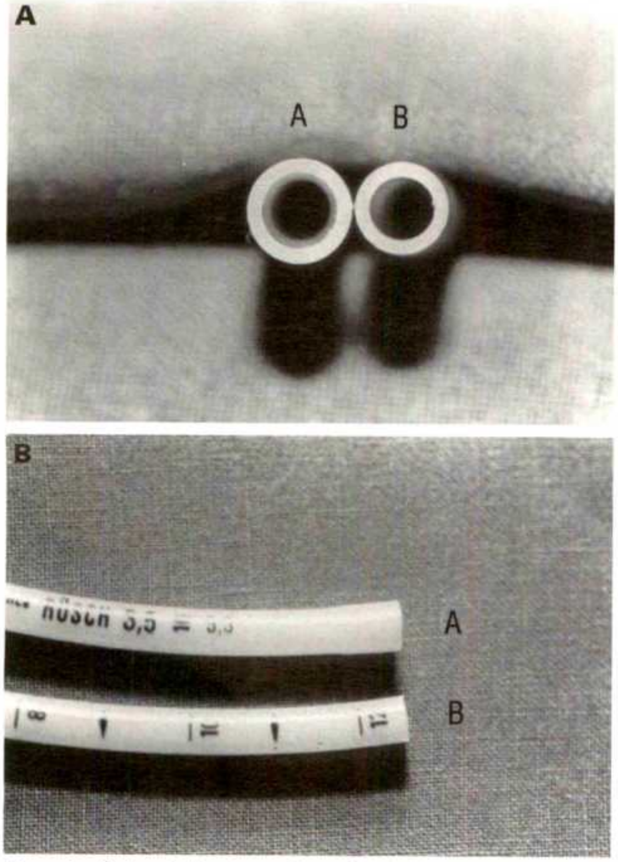

Figure 1 End and side views of an original (A) and manually cut (B) paediatric tracheal tube. Note the different internal diameters.

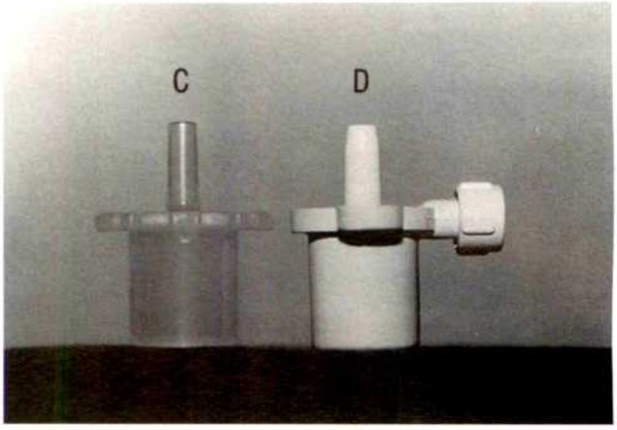

Figure 2 C=Plastic 15-mm connector with a vulnerable tube section provided with a commercially available paediatric 3.5-mm id tracheal tube. D=Special paediatric airway adapter, 3.5 mm id, with a resistant tube section and integral luerlock port.

Subsequent careful inspection of pre-packed paediatric tubes (Rusch, Waiblingen, Germany; Portex Ltd, Hythe, England; Mallinckrodt Medical UK Ltd) showed that: (1) the proximal end of all commercially available paediatric tubes is pre-widened by the manufacturer (e.g. 6–8 mm of a 3.5-mm id TT is pre-widened to approximately 4.5 mm id) (fig. 1); and (2) the tube section of the plastic 15-mm connector is thin and vulnerable (fig. 2).

Thus while it is very easy to insert the original plastic 15-mm connector into the original pre-widened paediatric TT, it requires a very smooth touch to insert the same connector without damage into a tube from which the pre-widened section has been cut away. In our case, the failed attempt to insert the 15-mm connector actually widened the proximal end of the cut tube sufficiently for another connector of equal size to be inserted without any damage.

With respect to our data, we strongly recommend moderately stretching the proximal end of cut tubes crosswise at 9 and 12 o'clock with, for example, an artery forceps or a similar instrument, to avoid damage to the plastic 15-mm connector while it is being inserted into the cut tube. To test the reliability of such self-widened cut tubes into which connectors had been inserted as described, we placed several under water, increased the pressure within them and found that the tubes were always airtight. The elasticity of the tube and the conical shape of the tube section of the connector both work to advantage here. Our method has worked without flaws in all subsequent operating room applications.

Another possibility of avoiding the critical incident described by Gupta and Harry[1] is to use a commercially available special paediatric airway adapter (available from 2.5–5.0 mm id; Ohmeda, Madison WI, USA) if the tube is to be cut. The tube part of this adapter is thick and resistant (see fig. 2) and can be inserted into a cut tube without damage. Nevertheless, here too widening of the cut paediatric tube as described above facilitates insertion of this special paediatric airway adapter. Additionally, this special paediatric airway adapter features minimal dead space and an integral luerlock port for sampling end-tidal values.

C. A. Preis
Department of Anesthesiology and General Intensive Care
University of Vienna
Vienna, Austria
I. S. Preis
Department of Anesthesiology,
University of Würzburg,
Würzburg, Germany

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British Journal of Anaesthesia 1997; 79: 693

BOOK REVIEWS

Positioning in Anesthesia and Surgery, 3rd Edn. J. T. MARTIN AND M. A. WARNER (editors). Published by WB Saunders, Philadelphia. Pp. 345; indexed; illustrated. Price £54.00

This is the third edition of a standard text, the first edition of which appeared almost 20 yr ago; it has undergone considerable revision with contributors being almost exclusively anaesthesiologists with no surgical contributors. The book contains 21 chapters, two forewords and three prefaces and aims to cover a "very important area of anesthesiologic practice" which may frequently be neglected by all except "risk managers, patients and their attorneys". The current interest in risk management should ensure a welcome for the third edition.

The chapters are divided into seven sections: general considerations contains an interesting essay on operating table design and reviews the cardiorespiratory effects of the supine position. The next section comprises four chapters and forms the major portion (25%) of the text, with discussion of dorsal decubitus positions. Most chapters follow a similar pattern, describing the establishment of the position, associated physiological changes and complications. Emphasis on physiology and complications forms the main thrust of the book. The line drawings are excellent, illustrating the anatomy of vulnerable nerve pathways. Lateral and prone positions form the next two single chapter sections followed by "special considerations", comprising a chapter on positioning extremities, mainly an account of the factors and mechanism of peripheral nerve injuries, and head and neck positions. Patient categories contains chapters on lithotripsy, obesity (more an account of potential problems unrelated to position), paediatrics, obstetrics and geriatrics. Consideration of positioning for regional anaesthesia is included. The final section on potential complications is the second largest in the book forming approximately 14% of the text but contains some repetition of parts of previous chapters. The final chapter, medicolegal considerations, while adopting inevitably a transatlantic leaning, offers some sound principles which deserve restatement, including for example the importance of contemporaneous documentation.

This book is very comprehensive and emphasizes again and again the important issues of physiological disturbances and potential harm to patients arising from positioning. Although not an essential purchase for the individual, every library or department should have a copy for access by both surgeons and anaesthetists. Make sure yours has one!

D. Fell

1997 Yearbook of Intensive Care and Emergency Medicine. J.-L. VINCENT (editor). Published by Springer-Verlag, Berlin. Pp. 921; indexed; illustrated. Price DM168.00.

Each year the intensive care community visits Brussels for the annual International Symposium on Intensive Care and Emergency Medicine started 17 yr ago by Jean Louis Vincent. The meeting has a deservedly high reputation with visiting speakers from around the world discussing areas of their particular expertise. When speakers are invited to attend they are also invited to contribute a chapter to the *Yearbook of Intensive Care and Emergency Medicine* which is published to coincide with each meeting. In Brussels, delegates receive a copy as proceedings of the meeting; others have to buy the yearbook but they do get good value.

The *1997 Yearbook of Intensive Care and Emergency Medicine* is the latest volume in the series. Written by contributors to the 1997 Brussels meeting it reflects the current state of intensive care. The book has 19 sections covering a range of subjects from basic mechanisms of sepsis through gut dysfunction to intensive care unit organization and ethics. Each section has several chapters which are up-to-date reviews of subjects close to the hearts of the authors.

The book is full of interesting points but some were compelling for me. There are many theories about the development of sepsis but two chapters present evidence that disordered apoptosis is involved. Apoptosis is the mechanism whereby old or dysfunctional cells die and are phagocytosed. Neutrophils normally undergo apoptosis without releasing cytokines or activating the phagocytes. If a dysfunctional neutrophil does not trigger the programmes for cell death or if it is not phagocytosed at the correct time, it may itself release cytokines or activate the phagocytes to do so. The chapters which present the hypothesis fit together several strands of the pathology of sepsis and SIRS.

No current intensive care book would be complete without mentioning nitric oxide, and this volume devotes a section to the subject. The chapter on the regulatory roles of nitric oxide, such as in microvascular and mucosal permeability, sets a challenge for the future—to understand the role of inducible nitric oxide synthase and why cells should need to produce excess nitric oxide quickly. This challenge is taken up in following chapters on cytokine regulation of inducible nitric oxide synthase and the role of peroxynitrite in the pathogenesis of shock. Nitric oxide binds to haemoglobin and there are two chapters on haemoglobin and sepsis. The way in which nitric oxide binds to haemoglobin depends on its state of oxidation. Oxyhaemoglobin binds nitric oxide to form methaemoglobin, while deoxyhaemoglobin forms nitrosylhaemoglobin. Cell-free haemoglobin has been studied in animals and found to reverse the hypotension of shock. Clinical studies in humans are needed but the few anecdotal reports are encouraging.

Not surprisingly, there are several sections on ventilatory support but the emphasis is on less invasive modes. Reflecting this there is a chapter on ventilation without a tracheal tube during cardiac arrest. This reviews the new recommendation of the European Resuscitation Council to decrease tidal volume to 0.5 litre when ventilating the lungs of a victim of cardiac arrest before intubation. It also recommends strategies to reduce the risk of gastric inflation in this situation Chapters on non-invasive ventilation and modes of ventilation suitable for spontaneously breathing patients whose tracheas are intubated continue this minimalist approach to ventilation. There are also chapters from the invasive extreme, including one on liquid ventilation. These chapters deal with the patient–ventilator relationship and approach ventilatory strategies not only from the ventilator point of view with emphasis on alveolar recruitment but also from the patient point of view with a review of the physiology of ventilation in the prone position.

These are some of the highlights of the book for me. Because different chapters are written independently by different authors, there is some repetition and inevitably the chapter quality is variable. The book does, however, give a worthwhile picture of the present state of intensive care medicine in addition to posing some questions which may be answered in future yearbooks. It provides a useful reminder for those who attend the Brussels meeting (you can never get to all the sessions) and an invaluable update for everyone else.

M. P. Shelly

Papers for publication and all editorial communications should be addressed to:
Dr J. M. Hunter,
Editor-in-Chief, *British Journal of Anaesthesia*,
University Department of Anaesthesia,
Royal Liverpool University Hospital,
The Duncan Building,
Daulby Street,
Liverpool L69 3GA.
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"I would have everie man write what he knowes and no more."—MONTAIGNE

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EDITORIAL I

Inhaled nitric oxide in acute respiratory failure

The use of inhaled nitric oxide in the UK is undoubtedly increasing. The survey by Cuthbertson, Stott and Webster[1] identified 65 adult and paediatric intensive care units (ICU) using nitric oxide, but this may be an underestimate as BOC, Messer and Linde Gas supply medical grade nitric oxide to more than 100 different sites, and the number is increasing. There are approximately 250 ICU in the UK, so this unlicensed therapy is now used by 25–33% of all UK ICU. The survey reported by Cuthbertson, Stott and Webster[1] showed that most units use inhaled nitric oxide to treat acute lung injury (ALI) or the acute respiratory distress syndrome (ARDS), pulmonary hypertension or complications of cardiac surgery.

Some of the centres supplied with nitric oxide and not identified by Cuthbertson, Stott and Webster[1] might be special care baby units. There is now solid evidence to support the use of nitric oxide in hypoxic respiratory failure in neonates, and in persistent pulmonary hypertension of the newborn (PPHN). These conditions overlap somewhat, as acute lung conditions in infants such as meconium aspiration cause pulmonary hypertension, and idiopathic persistent pulmonary hypertension of the newborn causes right to left extrapulmonary shunting and hypoxaemia. In a study published earlier this year,[2] nitric oxide was compared with placebo in a multicentre, randomized, blinded, controlled study. A total of 235 infants were studied. Although there was no difference in mortality, there was a 28% reduction in the number of infants who required extracorporeal membrane oxygenation (ECMO) in the group treated with nitric oxide. In the same edition of the *New England Journal of Medicine*, a randomized, controlled, blinded study of 58 term infants with PPHN showed a 44% reduction in the need for ECMO, but again no difference in mortality.[3]

As neonatal ECMO alone almost certainly reduces mortality in infants with hypoxic respiratory failure,[4] these studies suggest that if oxygenation is supported in these infants, either with ECMO or inhaled nitric oxide, mortality will be lower than in infants receiving neither of these treatments, but that nitric oxide and ECMO are probably equally effective. This is reinforced by the observation that the causes of death of infants dying in the nitric oxide and control groups were similar. However, the advantages of inhaled nitric oxide treatment over ECMO are considerable: it is cheaper, simpler and probably does not need to be confined to specialist centres so avoiding complex inter-hospital transfers. The results of these two studies will probably be sufficient for the FDA to issue a licence for the use of nitric oxide in neonatal hypoxic respiratory failure in the USA. Whether or not inhaled nitric oxide produces less long-term morbidity than ECMO is still under investigation; a 2-yr follow-up of patients from one of these studies is planned, because the long-term effects of inhaled nitric oxide are unknown and ECMO may produce neurological sequelae not apparent at the time of treatment.

The situation in adults is far less clear. Although ECMO can reduce deaths from hypoxic respiratory failure in neonates, the only two large randomized studies of extracorporeal gas exchange in adult severe acute respiratory failure showed no benefit[5 6] which implies that in this group of patients, supporting oxygenation with more than standard treatments may not reduce mortality. Before the neonatal studies were published the effect of nitric oxide on the use of neonatal ECMO was already suspected, because audit data from ECMO centres showed a declining use of this treatment parallelling the increase in the use of inhaled nitric oxide but there are no similar data which might predict the value of nitric oxide in adults. Randomized, controlled studies of the effect of inhaled nitric oxide on mortality from acute respiratory failure have not yet been published. In the USA, a dose-ranging study of nitric oxide in ARDS sponsored by Ohmeda is now complete but the subsequent randomized controlled study is still underway and only interim results are available.[7] Recruitment to this study is slower than expected. The pan-European study of inhaled nitric oxide in ARDS sponsored by AGA (a Swedish gas supply company) has been stopped, because of poor recruitment and technical problems with some of the delivery devices. A multicentre study is also underway in France, but no results are available at present. Thus currently there is no clear demonstration of any improvement in mortality in adults with ARDS treated with nitric oxide.

The use of mortality as an end-point in studies of nitric oxide may not be appropriate because death caused by hypoxaemia or right heart failure is not common in the ICU, even in patients with severe ARDS. ARDS is not a condition that occurs in isolation, it is a pulmonary complication of a primary problem. Patients usually die *from* their primary condition with ARDS, not *from* ARDS, and so using nitric oxide to treat this condition may not have a major impact on mortality. This is analogous to the situation in the studies on neonates, where death caused by hypoxaemia was relatively uncommon because ECMO was available, and so nitric oxide had no effect on mortality. However, unlike the use of ECMO in neonates, in adult studies of inhaled nitric oxide an alternative end-point to mortality is not so obvious. Number of days undergoing ventilation is often used as a secondary outcome measure, but there is no clear pathophysiological reason why nitric oxide should lessen the duration of artificial ventilation and the only published data supporting this is a case report.[8] There is no doubt that nitric oxide improves arterial oxygen tension; in the 30 acute "before and after" studies of inhaled nitric oxide in acute respiratory failure published to date, either Pa_{O_2} increased with inhaled nitric oxide by an average of 11.3 kPa, or the Pa_{O_2}/FI_{O_2} ratio increased by an average of 8.7 kPa. There are no studies which show a decrease in Pa_{O_2}. These studies also showed an average reduction in mean pulmonary artery pressure of 4 mm Hg. However, these physiological changes are of little value unless they lead to reductions in mortality, morbidity or duration of stay in the ICU or hospital.

In addition to the problems outlined above, there are also practical problems of study design which may make it difficult to demonstrate a reduction in mortality in adult patients treated with nitric oxide. As only approximately 65% of patients with ARDS show an appreciable increase in arterial oxygenation on inhaling nitric oxide,[7] any study that is totally blinded must have a large number of "non-responders" in the treatment group, and assuming that any reduction in mortality results from an increase in oxygenation, this dramatically reduces the power of the study to detect a change in mortality. This can be countered by increasing the number of patients studied, or by limiting the study to patients who show a suitable response to a test dose. However, limiting the study to patients who respond makes blinding virtually impossible and nitric oxide would be denied to half of the patients who show a response to a test dose. While this is ethically acceptable, because there is no clear long-term benefit from inhaled nitric oxide, practically it would be difficult to withhold nitric oxide from an individual patient with critical oxygenation who showed a dramatic response, especially in an ICU which already uses nitric oxide.

If the large study in the USA shows a clear reduction in mortality when nitric oxide is used to treat ARDS the drug will probably receive a licence from the FDA for adult use, and the Medicines Control Agency in this country might well follow the FDA's lead. However, if the study shows little or no effect a confusing situation will result. A drug will be in use in a large number of ICU in the UK which cannot be shown to be beneficial in a large study, but which individual clinicians believe can be life-saving in certain circumstances. There may be unavoidable flaws in the design of the study, making the negative result less than clear-cut. The company that supplies most of the drug in the UK (BOC) has elected not to charge for it while it is an investigational compound, and so will be losing money, and the patent protection for the product may not be watertight. In this circumstance they might not wish to fund further expensive large scale studies. However, as nitric oxide is now used widely, it would be difficult to cease to supply it to clinicians who believe it is beneficial. The way forward from this scenario is not clear.

J. D. YOUNG
Nuffield Department of Anaesthetics
Radcliffe Infirmary
Woodstock Road
Oxford OX2 6HE

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EDITORIAL II

"Ecstasy" and the anaesthetist

The drug commonly known as "Ecstasy" is now an omnipresent part of "youth culture" and scarcely a week passes without its mention in the national press, either directly or indirectly associated with death or injury or in relation to some criminal activity. While its proponents claim that it is relatively safe (it is widely perceived as "safer than alcohol") others point to evidence of potential long-term neuropsychiatric morbidity in addition to its acute dangers.

Management of the acute manifestations of Ecstasy poisoning may often fall to the anaesthetist, both in the emergency room and in the intensive care unit. The chronic effects may not pose such a problem, although the profound "hangover" effects of Ecstasy, often lasting 4–5 days, may have implications for the care of patients undergoing elective surgery within this period.

Ecstasy (3,4-methylenedioxymethamphetamine, MDMA, "E", "XTC", "Adam") resembles chemically a combination of amphetamine and mescaline. Its "sister" drug, 3,4-methylenedioxyethamphetamine (MDEA, "Eve") and metabolite 3,4-methylenedioxyamphetamine ("Ice") have been reported to have similar effects.[1–3] MDMA was first produced in 1914 by Merck and used as an appetite suppressant. It was abandoned but subsequently rediscovered in the 1970s when it was used as an adjunct to psychotherapy (making use of the sense of empathy, energy and euphoria as an aid to communication).[1] The commonly experienced effects of MDMA have been described by Peroutka, Newman and Harris after a survey of 100 regular users on an undergraduate campus. They include empathy (90%) and heightened alertness (50%), but also trismus (75%), tachycardia (72%) and bruxism (65%); 67% reported that the positive effects lessened with regular use, while negative effects increased.[4] A recent study by Curran and Travill examined the hangover effects in regular users and found that while a comparable group of alcohol users had recovered after 1 day, MDMA users experienced marked depression and impaired attentional/working memory task performance some 5 days later.[5] MDMA is known to cause release of 5-hydroxytryptamine (5-HT), one of the neurotransmitters implicated in the control of mood[6]; it has also been shown in primates to result in permanent loss of some serotonergic nerve fibres.[7] This has led to the suggestion that regular MDMA use may predispose to long-term neuropsychiatric morbidity. There have been several case reports of the precipitation of acute psychoses by abuse of MDMA.[8 9]

MDMA first became popular as a drug of abuse in the late 1980s. It was listed as a class A drug in the UK in 1977 and banned in the USA in 1985. The first recorded fatality occurred in the USA[1] but many have since occurred in the UK. It has been suggested that this reflects a difference in the pattern of usage.[2] While in the USA, MDMA had been used in a "party" setting, in the UK it found popularity as a "dance drug". This trend, however, has now occurred in the USA. It is used at "raves" where energetic dancing at close quarters for many hours may facilitate development of hyperpyrexia.

The principal acute danger of MDMA is its association with a gross hyperpyrexial reaction and subsequent rhabdomyolysis, disseminated intravascular coagulation and multiple organ failure (MOF). The thermoregulatory centre in the preoptic area of the hypothalamus is known to respond to 5-HT by increasing body temperature (through vasoconstriction, increased muscle tone and shivering, etc.). 5-HT is also implicated in the hypothalamic response to bacterial pyrogens resulting in a shift in the temperature "set-point" during a febrile episode.[10] MDMA is thought to induce marked hyperpyrexia through central mechanisms involving 5-HT$_2$ receptors. It has been shown that agents blocking 5-HT uptake can prevent the acute release and depletion of 5-HT by MDMA.[6] The syndrome of hyperthermia associated with MDMA bears great similarity to that of severe heat stroke, the neuroleptic–malignant syndrome, the serotonergic syndrome and to malignant hyperthermia. This may reflect the final common pathway associated with the consequences of gross hyperthermia. The apparently idiopathic nature of the full acute response may be explained by the presence of some form of metabolic myopathy, as has been suggested in the context of those individuals prone to heat stroke.[11]

The usual presentation in cases of acute toxicity is of hyperthermia, muscle rigidity, obtunded consciousness and in many cases fitting. There appears to be no relation to dose; it may not be the patient's first exposure and others taking from the same supply may be unaffected. The patient may deteriorate rapidly towards MOF, requiring intensive support of cardiovascular, respiratory and renal systems. Five or more organ-system failure has been described, while some such cases have survived.[12 13] Mortality appears to relate to the extent and duration of hyperthermia; the maximum temperature described for a subsequent survivor was 42 °C.[14] All would agree that rapid cooling measures are essential together with support of failing organ systems. Dantrolene has been used to aid control of hyperpyrexia and is recommended by Guy's Poisons Unit (July 1997: if temperature >40 °C). Some authors have doubted its value partly because it treats effect and not cause. The Heatstroke Centre in Makkah, Saudi Arabia, has reported that dantrolene is of no benefit in the treatment of severe heat stroke.[15] In this experienced unit, they were able to study 52 patients over a 4-day period in a randomized, double-blind, controlled study and found that dantrolene had no effect on the rate of cooling. They are however well practised and have equipment for patient cooling not commonly available in the UK. It must also be remembered that heat stroke is a different entity in which the normal thermoregulatory mechanisms have been overwhelmed. In MDMA reactions the thermoregulatory mechanisms may be abnormal. If one considers the most markedly pyrexial cases detailed in the literature, but exclude those with peak temperatures of 42 °C (only one reported survivor[18]) or more, there is some suggestion that dantrolene may be of benefit. Peak temperatures in the range 41–41.9 °C have been associated with four of four survivors in the dantrolene treated group and two of five in the non-dantrolene treated group.[2,12,13,16–19] If this range is broadened to 40–41.9 °C then there were 10 of 10 survivors who received dantrolene compared with six of 10 who did not.[2,3,17,19–24] It has been noted that rapid control of temperature was produced in cases where dantrolene was used.[14,21] In most centres, where a patient is *in extremis*, requiring intubation, ventilation, transfer to intensive care facilities and invasive monitoring and support, any aid to cooling at this busy time may be of benefit.

Awareness of the danger of hyperthermia among users of MDMA has led to the practice of drinking large volumes of water at "rave" parties to prevent the compounding effect of dehydration. Death after MDMA has also been reported to be a consequence of dilutional hyponatraemia and cerebral oedema caused by excessive water intake. This may also be associated with the inappropriate production of antidiuretic hormone.[25,26] Isolated hepatic failure in the absence of preceding MOF has also been reported. It is unclear if this represents a reaction to a contaminant or possibly an idiosyncratic reaction to the MDMA itself.[27]

MDMA has been implicated as a precipitant to deaths from pre-existing heart disease such as cardiomyopathy and, in common with other drugs of abuse, as a contributing factor to accidents and trauma.[1]

MDMA and the consequences of its use may be with us for some time, and the size of the problem associated with chronic use cannot yet be assessed. The manifestations of acute toxicity will continue to present, and a controlled study of such cases will almost certainly require national coordination if further progress is to be made in their treatment.

A. P. HALL
Department of Anaesthesia
Leicester Royal Infirmary
Leicester LE1 5WW

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CLINICAL INVESTIGATIONS

The intubating laryngeal mask. I: development of a new device for intubation of the trachea

A. I. J. BRAIN, C. VERGHESE, E. V. ADDY AND A. KAPILA

Summary

The standard laryngeal mask airway (LMA) functions both as a ventilatory device and as an aid to blind/fibrescopic-guided tracheal intubation. We describe the radiological and laboratory work used to bioengineer a new laryngeal mask prototype, the intubating laryngeal mask airway (ILMA). The aim was to create a new airway system with better intubation characteristics than the LMA. Other design goals were to eliminate the need for head–neck manipulation and insertion of fingers in the mouth during placement. Development was aided by analysis of magnetic resonance images of the human pharynx and laboratory testing with a variety of tracheal tubes. The principal features of this new system are an anatomically curved, rigid airway tube with an integral guiding handle, an epiglottic elevating bar replacing the mask bars, a guiding ramp built into the floor of the mask aperture and a modified silicone tracheal tube developed for use with the device. (*Br. J. Anaesth.* 1997; **79**: 699–703).

Key words
Equipment, masks anaesthesia. Intubation tracheal. Intubation tracheal, technique.

Tracheal intubation using a laryngoscope inevitably involves distortion of the anatomy in order to bring the glottis into the line of sight. In addition, the tracheal tube (TT) is designed for ease of passage when the anatomy is thus distorted and as a result its curvature does not correspond with the contours of the relaxed anatomy of the upper airway. Because it is not always possible or desirable to distort the anatomy, the difficult airway remains an important cause of mortality and morbidity in anaesthesia[1] in spite of a plethora of intubating aids and difficult airway algorithms.[2] The laryngeal mask airway (LMA) has found a place in this arena[3] but suffers from the disadvantages that its airway tube permits only up to a 6 mm TT and is too long to ensure the cuff of the TT does not come to lie between the vocal cords.[4] Further, the tube is not sufficiently rigid to permit manipulation to bring the mask into alignment with the glottis and cannot be removed easily from the TT when intubation has been accomplished.[5] In addition, the mask aperture bars (MAB) may obstruct passage of the TT. Nevertheless, it has the advantage that ventilation can be maintained whether or not the patient's trachea can be intubated. This advantage seemed sufficiently important to justify modification of the standard device to create a more appropriate intubating tool.

The first modification incorporated a change to the LMA airway tube only and has been described elsewhere.[6] We describe how bioengineering principles were applied to the further development of the intubating laryngeal mask airway (ILMA) using magnetic resonance imaging (MRI) and other laboratory work. The aim of the developmental process was to create a new intubating system with better insertion and intubation characteristics by making the ILMA more compatible with oropharyngeal anatomy and identifying a suitable TT for use with the device.

Methods

THE AIRWAY TUBE

Figure 1 shows how the airway tube has been modified in the new version of the ILMA. The form of the tube was derived from head and neck sagittal magnetic resonance imaging (MRI) views in 50 normal subjects whose heads were held in a neutral position (fig. 2) and differs from that described in an earlier study.[6] Ethics Committee approval was not sought as the images had already been taken for clinical reasons unrelated to the airway; confidentiality was maintained. The convex radius of the curve of the metal tube (41.5 mm) represents a value close to the best fit curve from the concave antero-posterior curves of the palato-pharyngeal arch which were traced from the MRI images. The tube is curved around a minimum arc of 128° corresponding to the approximate alignment of the distal end with the glottic axis measured from the MRI images. The minimum internal diameter (id) of the tube was

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A. I. J. BRAIN, MA, LMSSA, FFARCS (I), Royal Berkshire Hospital, Reading and Institute of Laryngology, University of London, London. C. VERGHESE, MB, BS, FRCA, A. KAPILA, BSC, MB, BS, FRCA, Department of Anaesthesia, Royal Berkshire Hospital, Reading RG1 5AN. E. V. ADDY, BSC, MB, BS, MRCP, FRCA, Oxford Radcliffe NHS Trust, Oxford. Accepted for publication August 6, 1997.

Correspondence to C. V.

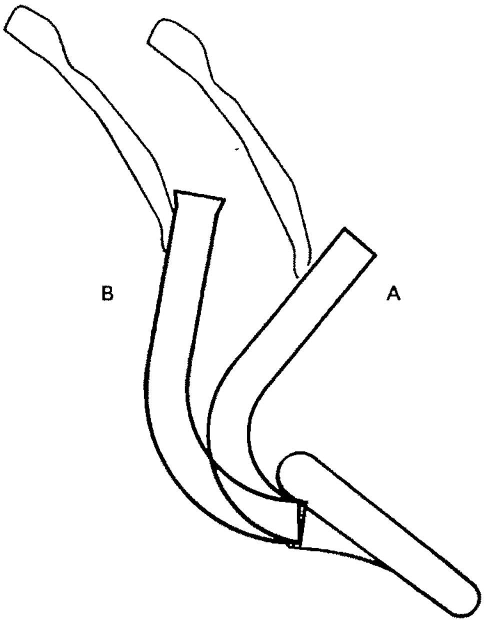

Figure 1 Airway tube: final form (A) and earlier prototype (B).

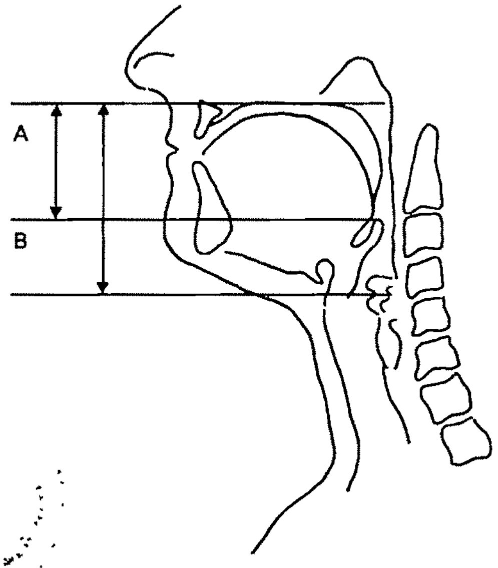

Figure 2 Typical saggital section MRI from which the following measurements were made: A=distance from the dome of the hard palate to the epiglottic tip (PE distance); B=distance from the dome of the hard palate to the arytenoid cartilage (PA distance).

chosen to be 13 mm, with a wall thickness of <1 mm. This accepted up to an 8.0 mm id cuffed TT. Wider tube diameters were found to be impossible to curve sufficiently tightly to meet the anatomical requirement using stainless steel and moreover could not be drawn down into the correct dimensions for a standard 15 mm outside diameter (od) connector. Stainless steel was chosen because of its compatibility with silicone, high strength (permitting a good id:od ratio), malleability (low risk of fracturing), ease of sterilization and cleaning, and absence of toxicity. To minimize trauma risk and facilitate secure bonding with the mask portion, the tube was covered with a silicone sheath giving an od of 17.6 mm, apart from its distal or outer end which was accurately pressed into a standard 15 mm connector shape. The maximum od (20 mm) occurs in the plane of the curvature of the tube at the point where it is overlapped by the proximal part of the cuff. Unlike the standard LMA tube, which had to protrude sufficiently from the mouth to be gripped easily and to permit stabilization by bending down over the chin, the rigid metal tube with its gripping handle could be made shorter, terminating close to the mouth. Thus the relative shortness and increased id of the tube allowed passage of an adult sized TT to its correct depth, overcoming the main disadvantage of the standard LMA as an intubating guide.

The stainless steel handle welded to the outer end of the tube proximal to the 15 mm connector facilitated device manipulation and made it possible to perform insertion without placing the fingers in the mouth. The handle was stiff but malleable, permitting some adjustment of the angle it made with the tube.

The distal end of the tube was not cut squarely but had a 30° bevel anteriorly, in order to permit compression of the device at its widest point for patients with reduced inter-dental distance.

EPIGLOTTIC ELEVATING BAR

As both the epiglottis and the bars across the LMA aperture may impede passage of a TT through the LMA,[7] the bars were replaced with a single central bar, or epiglottic elevating bar (EEB), attached only at the upper rim of the mask so that its free end could be swung out by the advancing TT, pushing the epiglottis out of the way as it did so. Critical to performing this function was the level of the EEB tip in the pharynx, as it has to lie deeply enough to engage with the epiglottis but not so deep that it became wedged posterior to the caudal rim of the glottic aperture. In order to arrive at the correct position and size of the EEB, the pharyngeal level of the epiglottis in each of the MRI views was measured. Epiglottic depth was expressed as the distance between the free end of the epiglottis and the dome of the hard palate (PE distance), measured along a line drawn parallel to the first five cervical vertebrae and a line at right angles to this line passing

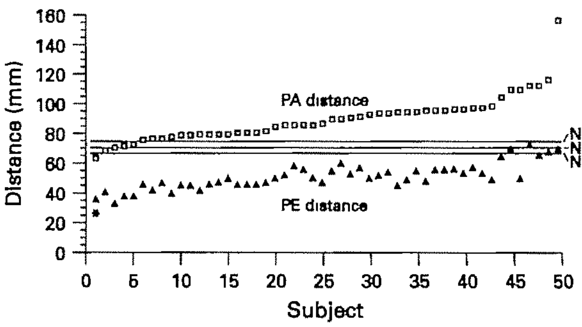

Figure 3 Palato-arytenoid distance (PA) and palato-epiglottic distance (PE) in each of the 50 MRI subjects. The gap between PA and PE represents the size of the glottic aperture in the cephalo-caudal axis. The horizontal lines represent distances of the tip of the epiglottic elevator bar (EEB) from the dome of the hard palate for the three sizes of the ILMA, measured along the same axis. In only one subject (*) was the glottic aperture too high for all three sizes of the LMA.

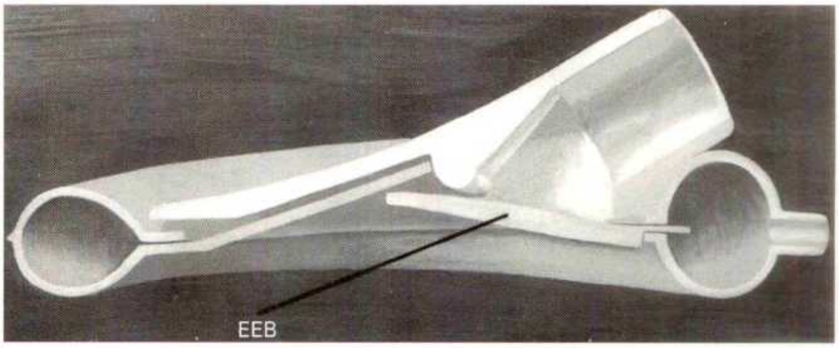

Figure 4 A prototype ILMA sectioned longitudinally in the mid-line to show the arrangement of the guiding ramp. EEB=Epiglottic elevator bar.

tangential to the dome of the hard palate. The distance between the hard palate and the arytenoid cartilages was also measured along the same axis (PA distance) (fig. 2). The length of the glottic aperture was then calculated (PA–PE). The length of EEB which would bring the EEB tip most reliably into a position behind the epiglottis where it could act as an epiglottic lever could then be determined. Keeping the size of the tube constant, three sizes of mask were used, into each of which an EEB was fixed proportional to the size of the mask. The mask sizes corresponded to sizes 3, 4 and 5 of the standard LMA. After tracing the predicted position of each mask size onto tracings of the MRI pictures, a suitable length of EEB was arrived at, such that the EEB tip rested at the approximate mid-point in the bowl of each size of mask. Assuming the airway tube lay in contact with the palatal dome, the relative distances from the tip of the EEB to the highest point or apex of the palatal dome for the three sizes of the ILMA were measured along the same axis as PE distance. These distances were 67, 71 and 75 mm for sizes 3, 4 and 5 ILMA, respectively. A plot of PE and PA measurements in the 50 subjects showed that for all except one subject the position of the EEB tip came to lie within the glottic aperture for at least one of the three sizes of ILMA (fig. 3).

TRACHEAL TUBE GUIDING RAMP

In order to direct the TT anteriorly as it emerged from the mask aperture, the passage immediately behind the EEB was provided with a 20° ramp in its floor (fig. 4). This gave a 47° angle with the plane of the mask cuff. The posterior floor of the ramp was contoured in a "V" instead of a "U" shape in order to centralize tubes passed through it irrespective of diameter; this avoided the problem of TT being deviated to the left or right when they impinged on the EEB.

TRACHEAL TUBE

Direct laryngoscopy requires distortion of the anatomy to obtain a line of sight from the mouth to the vocal cords. The TT has traditionally been shaped to facilitate its placement when the head, neck and anterior pharyngeal structures have been distorted. On encountering the laryngeal inlet, a TT is required to reverse its curvature by approximately 30° from the plane of the inlet to pass into the trachea. In view of this it was clearly undesirable to use a TT the natural curvature of which was in the reverse direction. Moreover, polyvinylchloride (PVC) TT were found to retain the additional curvature imposed on them by the ILMA tube. Bench testing using standard PVC TT showed that PVC significantly retained the curvature imposed by passage through the metal tube and that this effect was retained even when the tubes were warmed to 37 °C (fig. 5). This effect was not seen with silicone tubes. Therefore, it appeared logical to use straight, soft, cuffed silicone TT when intubating through the ILMA device. Accordingly, prototype 8 mm id cuffed silicone TT were prepared (Accusil Inc, IN, USA). These were marked transversely with a depth marker to show the user the point at which the tip of the TT was about to lift away the EEB. In addition, a longitudinal line similar to the black line on an LMA tube was provided to serve as a guide to the

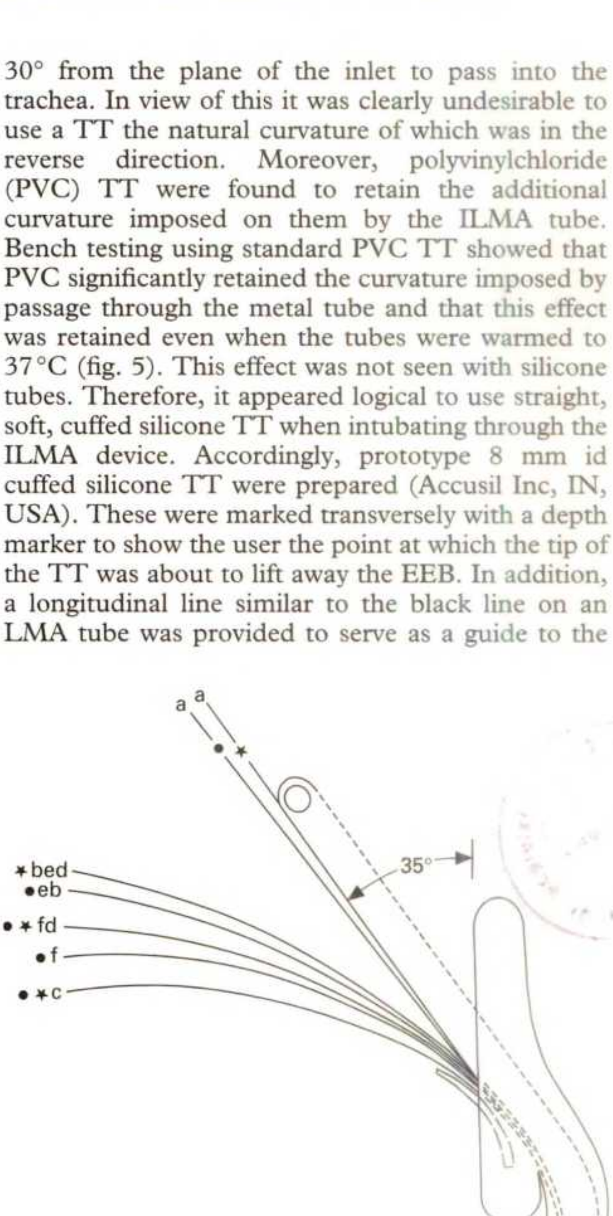

Figure 5 Effect on tracheal tube curvature for different tubes at 25 °C (●) and 37 °C (★) when passed through the ILMA tube: a=straight silicone 8 mm; b=curved Euromedical PVC 8 mm; c=Rusch red rubber 8 mm; d=Portex PVC 8 mm; e=Mallinkrodt PVC 8 mm; and f=Mallinkrodt PVC reinforced 7 mm.

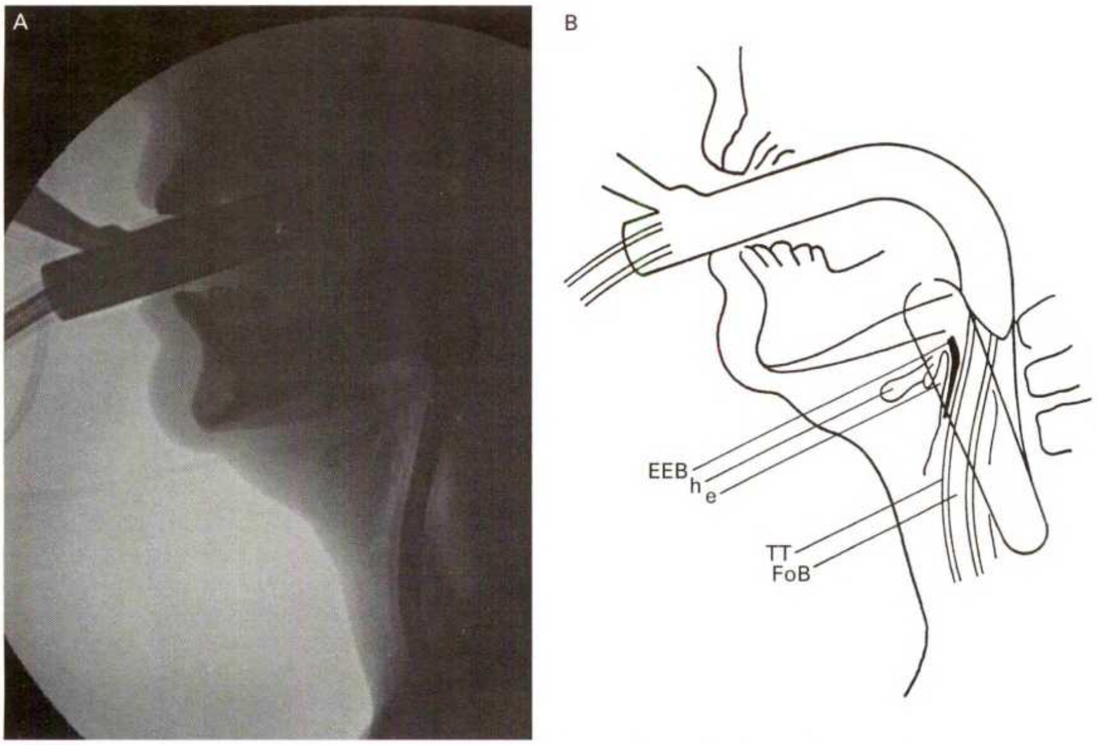

Figure 6 Soft tissue radiograph with explanatory drawing of a patient's trachea intubated through the ILMA. A fibreoptic scope had been passed through the straight silicone tube subsequently. EEB=Epiglottic elevator bar; h=hyoid; e=epiglottis; TT=straight silicone tracheal tube; and FoB=fibreoptic bronchoscope.

orientation of the TT bevel. The pilot balloon and valve were small enough to pass easily through the metal tube of the ILMA, and the TT connector was removable (standard connectors are too large to pass through the ILMA tube) in order that the ILMA could be removed from the patient when intubation has been achieved.

Figure 6 is a soft tissue radiograph with explanatory drawing showing a patient's trachea intubated through the device using a silicone tube, through which a fibrescope has been passed. The EEB can be seen displacing the epiglottis anteriorly.

Discussion

We have described the further development of an ILMA prototype to aid tracheal intubation.

Our initial studies with a modified LMA[6] indicated that with manipulation of the head and neck it was possible to place a TT blindly while maintaining ventilation by connecting the TT to the anaesthesia system. With the further development of the ILMA, several potential advantages compared with conventional laryngoscopy and intubation are apparent. The standard tracheal tube is subject to distortion stresses when in place which, as Lindholm pointed out, are transmitted to the anatomy.[8] This factor combined with the distortion stresses inherent in laryngoscopic manipulation make it unsurprising that the conventional practice of tracheal intubation is associated with significant morbidity.[9] The ILMA design allows a soft, flexible, silicone tube to be directed towards the plane of the glottis without distortion of the anatomy. Further, the ILMA is inserted without manipulation of the head and neck.

Circulatory responses to direct laryngoscopy and tracheal intubation were first described in 1951[10] and since then much work has focused on ways to attenuate these responses. It has been shown that placement of the LMA is associated with a reduced stress response compared with the TT[11 12] and this may be advantageous in those patients likely to be adversely affected, such as those suffering from hypertension or ischaemic heart disease, or both. It is possible that tracheal intubation through the ILMA may be less stimulating than conventional laryngoscopy, but this remains unsubstantiated. Ease of placement without head and neck manipulation and without the need for the rescuer to be positioned behind the head or to insert fingers into the mouth, together with its ability to serve as a sole airway suggest a role in emergency medicine. This role is made more attractive by the possibility of subsequently being able to insert an appropriate sized TT through the device without first having to remove it. Finally, inability to ventilate a patient's lungs during attempts at TT placement remains an unsolved problem in anaesthesia. We believe this ILMA prototype has the potential to help alleviate this problem, not only by permitting continued ventilation during intubation attempts, but because avoidance of the need to obtain a line of sight should in theory eliminate the major cause of such difficulties. Our preliminary clinical experience with this device in 150 patients with routine and abnormal airways is reported subsequently.[13]

Acknowledgement

We thank the Department of Radiology at the Royal Berkshire Hospital for their assistance in making available the MRI and Dr J. Brimacombe for advice.

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British Journal of Anaesthesia 1997; **79**: 704–709

The intubating laryngeal mask. II: a preliminary clinical report of a new means of intubating the trachea

A. I. J. BRAIN, C. VERGHESE, E. V. ADDY, A. KAPILA AND J. BRIMACOMBE

Summary

We have assessed the efficacy of a new laryngeal mask prototype, the intubating laryngeal mask airway (ILMA), as a ventilatory device and blind intubation guide. The ILMA consists of an anatomically curved, short, wide bore, stainless steel tube sheathed in silicone which is bonded to a laryngeal mask and a guiding handle. It has a single moveable aperture bar, a guiding ramp and can accommodate an 8 mm tracheal tube (TT). After induction of anaesthesia with propofol 2.5 mg kg^{-1} and fentanyl 2.5 μg kg^{-1}, the device was inserted successfully at the first attempt in all 150 (100%) patients and adequate ventilation achieved in all, with minor adjustments required in four patients. Placement did not require movement of the head and neck or insertion of the fingers in the patient's mouth. Blind tracheal intubation using a straight silicone cuffed TT was attempted after administration of atracurium 0.5 mg kg^{-1}. If resistance was felt during intubation, a sequence of adjusting manoeuvres was used based on the depth at which resistance occurred. Tracheal intubation was possible in 149 of 150 (99.3%) patients. In 75 (50%) patients no resistance was encountered and the trachea was intubated at the first attempt, 28 (19%) patients required one adjusting manoeuvre and 46 (31%) patients required 2–4 adjusting manoeuvres before intubation was successful. There were 13 patients with potential or known airway problems. The lungs of all of these patients were ventilated easily and the trachea intubated using the ILMA. In 10 of 13 (77%) of these patients, no resistance was encountered and the trachea was intubated at the first attempt; three of 13 (23%) patients required one adjusting manoeuvre. Tracheal intubation required significantly fewer adjusting manoeuvres in patients with a predicted or known difficult airway ($P<0.05$). We conclude that the ILMA appeared on initial assessment to be an effective ventilatory device and intubation guide for routine and difficult airway patients not at risk of gastric aspiration. (*Br. J. Anaesth.* 1997; **79**: 704–709).

Key words
Equipment, masks anaesthesia. Intubation tracheal. Intubation tracheal, technique.

Tracheal intubation using a laryngoscope involves distortion of the anatomy in order to bring the glottis into the line of sight. Sufficient anatomical distortion is not always easy or possible, leading to intubation difficulties in 1–3%[1] and failure in 0.05–0.2% of cases.[2 3] Failed/difficult tracheal intubation remains an important cause of mortality and morbidity in anaesthesia.[4] The laryngeal mask airway (LMA) has an established role in the management of failed intubation.[5 6] Difficulty in viewing the glottis is generally irrelevant for successful LMA placement, making it a useful substitute airway, and the curved tube guides instruments towards the glottis, making it a useful intubation aid. Reported success rates for blind and fibreoptic-guided passage of a tracheal tube (TT) via the LMA vary between 30–93%[7–9] and 96–100%,[10–12] respectively, depending on technique, experience, number of attempts taken and equipment chosen. However, the standard LMA is not an ideal intubation aid as the airway tube is too narrow to accommodate an adult diameter TT, too long to ensure a normal length TT will reach the trachea and not sufficiently rigid to function as a guide to exact alignment of the mask with the glottis. In addition, the mask aperture bars may obstruct passage of the TT. In an attempt to overcome these limitations, a prototype intubating laryngeal mask airway (ILMA) has been developed. Other design goals were to eliminate the need for head–neck manipulation and insertion of fingers in the mouth during placement.

The following preliminary study assesses the safety and efficacy of the ILMA as a ventilatory device and blind intubation guide in patients with normal and abnormal airways.

Methods

APPARATUS

The prototype ILMA is shown in figure 1. The design features and objectives are given in table 1.

A. I. J. BRAIN, MA, LMSSA, FFARCS (I), Royal Berkshire Hospital, Reading and Institute of Laryngology, University of London, London. C. VERGHESE, MB, BS, FRCA, A. KAPILA, BSC, MB, BS, FRCA, Department of Anaesthesia, Royal Berkshire Hospital, Reading RG1 5AN. E. V. ADDY, BSC, MB, BS, MRCP, FRCA, Oxford Radcliffe NHS Trust, Oxford. J. BRIMACOMBE, MB, CHB, FRCA, MD, University of Queensland, Cairns Base Hospital, Cairns, Australia. Accepted for publication: August 6, 1997.

Correspondence to C. V.

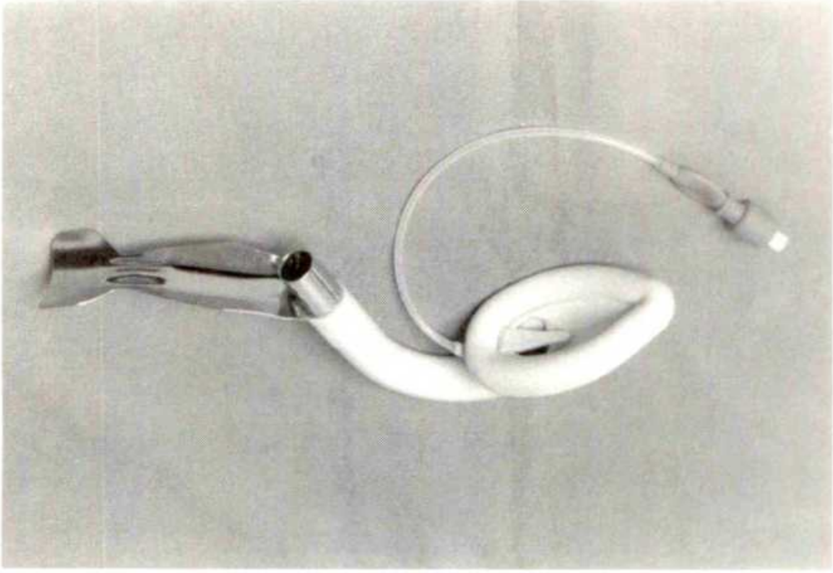

Figure 1 Prototype intubating laryngeal mask.

Table 1 ILMA design features and function

Feature	Function
Rigid stainless steel airway tube	Permits mask to be guided/steadied during intubation Short enough to permit TT to pass to correct depth Good internal: external diameter ratio (13:15 mm) Autoclavable
Integral 15 mm connector	Permits use as standard LMA Avoids danger of accidental disconnection Permits passage of 8.0 mm cuffed TT
Anatomical curve of tube	Permits insertion with mask following same path as with standard insertion technique Avoids need for head and neck manipulation Avoids need to insert finger because pressure against palate can be applied externally Aligns TT to plane of glottic vestibule Permits use of straight TT reducing anterior tracheal wall trauma
Integral tube handle	Allows device manipulation and steadying during intubation–extubation Facilitates device insertion–removal
Bevel on proximal end of stainless steel tube	Permits mask aperture to be compressed to permit passage via narrow inter-dental gap
"V"-shaped TT guiding ramp	Tube centring function Guides tube anteriorly to reduce risk of arytenoid trauma–oesophageal placement
Epiglottic elevating bar (EEB)	Acts as epiglottic ramp during insertion Keeps epiglottis from obstructing airway Protects and elevates epiglottis during tube passage

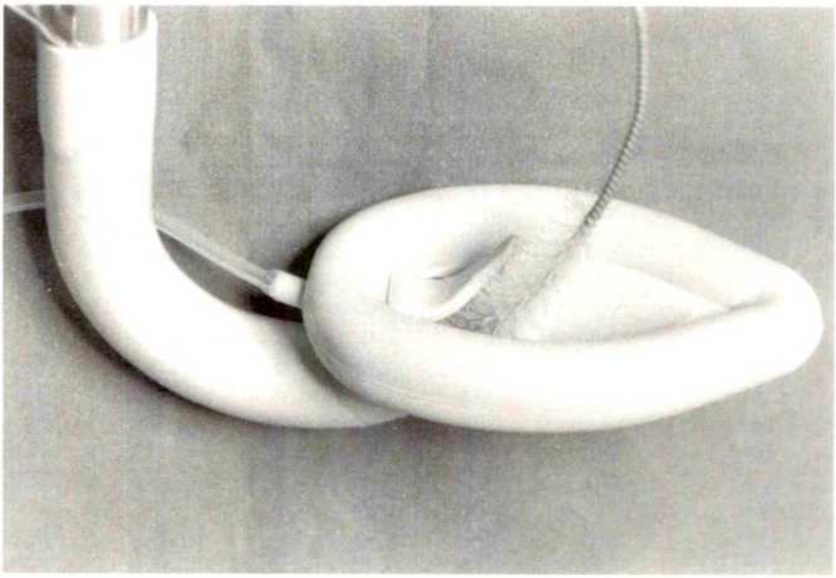

Figure 2 Epiglottic elevator lifted forward by cleaning brush.

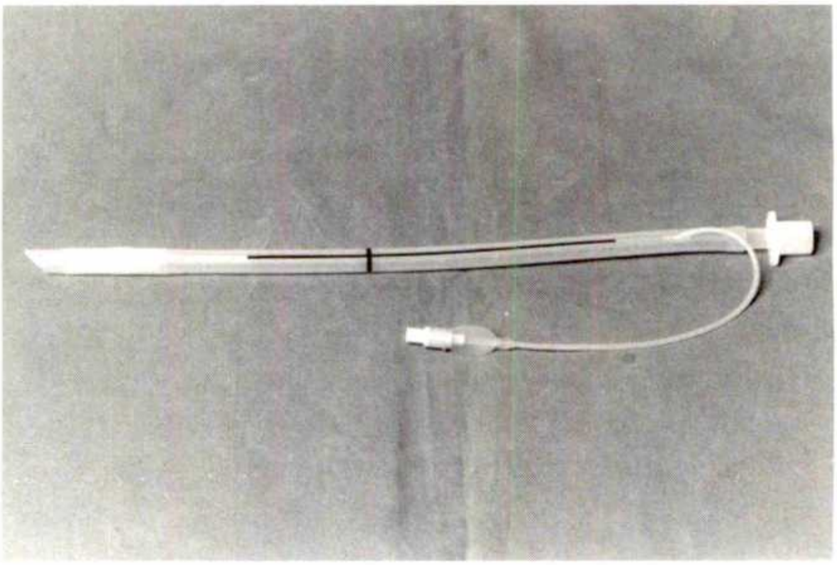

Figure 3 Prototype cuffed silicone tube used in the study.

The form of the tube was derived from MRI studies of 50 normal subjects and differs from that described in an earlier study.[13] Details on design and development of the ILMA and TT are presented in an accompanying article.[14] In brief, the new prototype device consists of an anatomically curved, short, wide bore, stainless steel tube sheathed in silicone which is bonded to a laryngeal mask and a guiding handle (fig. 1). It has a single moveable epiglottic elevator bar (EEB) (fig. 2), a guiding "V"-shaped ramp and can accommodate an 8 mm TT. The TT selected was a prototype straight cuffed silicone tube (Accusil Inc, IN, USA) which was marked transversely to show the user the point at which the tip was about to lift away the EEB (fig. 3). This marker was used as a reference point when measuring the depth at which resistance was felt during insertion. In addition, a longitudinal line similar to the black line on an LMA tube was provided to serve as a guide to the orientation of the TT bevel. With this line facing cephalad, the tube bevel faced to the left.

CLINICAL STUDY

This multicentre study received Ethics Committee approval and informed consent was obtained from all patients. We studied 150 patients undergoing general, orthopaedic or peripheral plastic surgery who required tracheal intubation. Patients were excluded if they were less than 18 or more than 90 yr of age, ASA IV–V, had respiratory tract pathology or were at risk of regurgitation–aspiration (previous upper gastrointestinal tract surgery, known or symptomatic hiatus hernia, oesophageal reflux, peptic ulceration or not fasted). Patients with potential or known airway problems with an inter-dental gap of >2.5 cm were recruited for the study where possible.

Standard monitoring was applied before induction and included ECG, pulse oximeter, capnography and non-invasive arterial pressure monitor. The lungs of all patients were preoxygenated for 3 min and fentanyl 2.5 μg kg^{-1} given i.v. followed 1 min later by propofol 2.5 mg kg^{-1} over 30 s. Patients' lungs were ventilated by face mask for 30 s with 100% oxygen and the ILMA inserted when the eyelash reflex was lost and the jaw relaxed. Additional boluses of propofol 0.5 mg kg^{-1} were given as required until an adequate level of anaesthesia was achieved for placement of the ILMA. Anaesthesia was maintained with isoflurane and nitrous oxide in oxygen. A size 4 and size 5 ILMA were available for the study. Size selection was at the discretion of the anaesthetist, but the size 4 was used for normal adults (30–70 kg) and the size 5 for large adults (>70 kg). All ILMA were inserted by experienced LMA users who had placed the ILMA on more than 10 occasions before the study.

The insertion technique consisted of a one-handed rotational movement in the sagittal plane with the head supported by a pillow to achieve a neutral position. Specifically, the mask was fully deflated with the rim facing posteriorly, a bolus of a water soluble lubricant applied posteriorly to the distal saucer-shaped tip, which was then flattened against the palate with no attempt made to push the device inwards until the saucer-shaped depression had been seen to be inverted against the palatal surface, drawing back slightly to ensure complete flattening of the rim into the dome of the palate. The ILMA was then rotated inwards, following the arc of the palate and posterior pharyngeal wall so that the curved tube remained closely applied to the inner aspect of the upper incisors throughout the insertion manoeuvre. After insertion, using a hand-held cuff inflator–manometer, the device was inflated to an intracuff pressure of 60 cm H_2O without holding it in place and ventilation was attempted by squeezing the reservoir bag. Successful placement–ventilatory ability was judged by chest wall movement and capnography (maintain PE'_{CO_2} within normal range) during manually assisted ventilation. If adequate ventilation was not possible the ILMA was manipulated *in situ* before removal and reinsertion.

When an adequate airway was established, patients were given atracurium 0.5 mg kg^{-1} and after

Table 2 Probable cause of resistance and appropriate management strategy at a variety of depths measured from the transverse marker on the tracheal tube (reflects distance of tracheal tube tip from bowl). EEB=epiglottic elevating bar, TT=tracheal tube, ILM=intubating laryngeal mask

Depth of resistance	Probable cause	Management
0–1.5 cm	EEB trapped behind cricoid cartilage	Use smaller ILMA
1.5–2 cm	Epiglottis down folded	TT removed. ILMA swung back outwards no more than 6 cm without deflating the cuff, then repositioned (up–down manoeuvre)
2–4 cm	EEB lying too high and unable to engage with the cephalad tip of the epiglottis	Use larger ILMA
4–6 cm	TT tip was wedged between the inflated mask tip and the cricoid cartilage	Use smaller ILMA

3 min the lubricated silicone TT was inserted into the metal tube of the ILMA, moving it up and down to distribute the lubricant until it was sliding freely, but without allowing the transverse line on the TT to pass within the metal tube. The TT was then connected to the anaesthesia breathing system to permit ventilation during and between intubation attempts. Tracheal intubation was attempted using a standardized design. The design was based on MRI data which suggested that different malpositions might be detected by noting the depth in relation to the transverse marker at which passage of the TT became blocked. An appropriate adjusting manoeuvre could then be attempted. After ensuring the longitudinal line on the TT was facing cephalad and grasping the handle of the ILMA to maintain it in the optimum ventilating position, the TT was passed carefully approximately 1.5 cm beyond the transverse marker. If no resistance was felt the downward movement of the TT was continued while observing signs of tracheal placement (end-tidal carbon dioxide trace and chest wall movement during ventilation). After inflating the TT cuff, manual ventilation was commenced gently and capnographic confirmation of TT placement was sought. In the absence of expired carbon dioxide, oesophageal placement was diagnosed and the tube removed immediately to re-establish ventilation through the ILMA. If resistance was felt the depth was noted and a variety of strategies were instituted based on probable cause (table 2). If the attempt failed, other manoeuvres were used including: optimizing the airway (steering the mask with the handle while squeezing the reservoir bag with the Heidebrink valve closed, until an optimal airway was obtained), raising the mask upwards, partial withdrawal, rotating the TT bevel, adjusting head–neck position or adding air to the cuff. When tracheal intubation was successful, the ILMA was removed using a 25 cm length tube, cut from an 8 mm silicone TT as a "pusher" to prevent accidental extubation while the device was being withdrawn.

The following data were recorded: age, weight, height, sex, potential or known airway difficulty, ILMA size used, number of attempts at ILMA insertion, airway complications during placement, ventilatory capability, number of adjusting manoeuvres (a maximum of four was considered an acceptable number in view of the potential of the device to permit continuous ventilation whether or not intubation succeeded), problems encountered and successful solutions during intubation, and problems with device removal. Finally, any episodes of oxygen saturation <95% were noted up to the point where the ILMA was removed and the TT secured.

Statistical analysis was with the Student's *t* test and chi-square test. Significance was taken as $P<0.05$.

Results

Mean age, height and weight were 56 (range 19–85) yr, 169 (153–188) cm and 73 (40–183) kg, respectively. The male:female ratio was 78:72. Placement of the ILMA was successful at the first attempt in all patients, but four (2.7%) required device repositioning to achieve adequate ventilation. There were no adverse airway events during placement. Tracheal intubation was successful in 149 of 150 (99.3%) patients: 75 (50%) at the first attempt, 28 (19%) required one adjusting manoeuvre, 21 (14%) required two, 18 (12%) required three and seven (5%) required four. Sizes 4 and 5 were used initially in 113 (75%) and 37 (25%) patients, respectively. On 10 (7%) occasions the size 4 was exchanged for a size 5 and on one (1%) occasion the size 5 exchanged for the size 4. Mean weight and height for the size 4 were 69 (range 40–183) kg and 164 (155–180) cm, respectively, and for the size 5, 85 (68–130) kg and 176 (158–188) cm, respectively.

Manoeuvres used to achieve successful intubation included: the up–down manoeuvre (61%), optimizing the airway (22%), change of size (7%), raising the mask upwards (4%), partial withdrawal (2%), rotating the bevel (2%), adjusting head–neck position (1%) and adding air to the cuff (1%). Oxygen saturation decreased to less than 95% after ILMA insertion on only two occasions. In one patient, a muscular man of 105 kg and height 153 cm, intubation attempts resulted in a decrease in saturation to 85% and further attempts were abandoned. The 25 min case was concluded using the ILMA as the sole airway. Oxygen saturation was maintained at 90%, but increased to normal levels during recovery, with no adverse sequelae. The second patient, a heavy smoking 146-cm, 76-kg female, developed bronchospasm during intubation attempts. Oxygen saturation decreased to 87% and resolved rapidly after deepening of anaesthesia. Intubation through the ILMA was accomplished easily and there were no further problems. No

Table 3 Patients with potential or known airway problems. *Unexpected failure to ventilate the lungs with face mask and Guedel airway before ILMA placement

	Type of airway problem
1	Cormack and Lehane III. Mallampati III. History of difficulty.
2	Cormack and Lehane III. Mallampati III. History of difficulty.
3	Cormack and Lehane III. History of difficulty.
4	Cormack and Lehane III, Mallampati IV. Poor mouth opening.
5	Limited neck movement (ankylosing spondylitis).
6	Cormack and Lehane IV. Mallampati IV.
7	Cormack and Lehane III.
8	Limited neck movement. Poor mouth opening (2.6 cm).
9	Cormack and Lehane III.
10	Cormack and Lehane III. History of difficulty.
11	Cormack and Lehane IV. History of difficulty.
12	Limited neck movement. (Obesity—183 kg).
13	Failed face mask ventilation*.

problems were encountered in removing the ILMA over the tube when tracheal intubation had been accomplished. No cases of major soft tissue damage or dental trauma occurred as determined by a lack of blood on removal of the device and routine postoperative questioning. The incidence of sore throat was not assessed formally.

There were 12 patients recruited with potential or known airway problems and one airway problem was encountered during the study (table 3). The lungs of all of these patients were ventilated easily using the ILMA and the trachea intubated subsequently through the ILMA without loss of airway control. In 10 of 13 (77%) patients, the trachea was intubated at the first attempt and in three of 13 (23%) patients one adjusting manoeuvre was required. The success rate of patients without a potential or known difficult airway was 65 of 137 (47%) at the first attempt. Tracheal intubation required significantly fewer adjusting manoeuvres in patients with a potential or known difficult airway (10 of 13 *vs* 65 of 137; chi-square=4.13, $P<0.05$).

Discussion

This preliminary unblinded study has shown that the ILMA is an effective ventilatory device and blind intubation guide for normal sized TT in anaesthetized patients with routine and difficult airways. The success rate as a ventilatory device (100%) was comparable with the standard LMA (>98%).[15–17] The success rate as a blind intubation guide (99%) was higher than the standard LMA (19–93%)[7–9 12] and an earlier prototype ILMA (93%),[13] and similar to fibreoptic-guided intubation via the standard LMA (97–100%).[10–12] Studies are currently underway to determine the success rate of the ILMA as an aid to fibreoptic-guided intubation.

It is likely that the procedure to determine the appropriate adjusting manoeuvres will be refined as experience increases. The tactic of optimizing the airway (first suggested by C. V.) was highly effective and may be a more logical approach than allowing the device to self-locate or changing size. It is possible that the "up–down" manoeuvre was beneficial not because the epiglottis was down folded, but because the larynx might have been initially displaced downwards. It is also possible that the TT bevel was catching on the lateral vestibular wall in some cases where epiglottic down folding was thought to be the cause of the problem. This does not appear to have occurred in earlier LMA studies[8 9] and may be because of the smaller diameter of tubes used with the standard device (sizes 3 and 4), as they are less likely to become caught against the glottic anatomy. A logical design modification would be to arrange for the bevelled tip of the TT to point in the mid-line or make the tip curved like a Tuohy needle and this has now been done. Another possible unrecognized cause of failure was the presence of a narrow epiglottis which might slip to one or other side of the EEB. This was observed fibreoptically by another investigator using an identical ILMA (D. Ferson, personal communication, MD Anderson Center, Houston, TX, USA).

The ILMA offers several advantages and disadvantages over the standard LMA. The ILMA overcomes the diameter–length limitations for TT imposed by the standard LMA and facilitates guidance of the TT towards the glottis. The ILMA does not require head–neck manipulation (use in cervical spine pathology) or insertion of the fingers in the patient's mouth (less risk for damaging the practitioners fingers–infection transmission) for successful placement. The insertion technique is conceptually simpler and may be achieved using the same rotational manoeuvre from any position (useful when access is limited). The wide, short tube should offer less work of breathing and allow passage of larger instruments into the respiratory tract. Although the fixed length and rigid tube means that the tip may not necessarily sit in the correct position, the guiding handle allows an optimal airway to be sought out and additional force applied to the periglottic tissues if a higher pressure seal is transiently needed. Other disadvantages are that the ILMA is unsuitable used alone for most head, neck, ENT and dental surgery (the handle sticks out and the wide rigid tube occupies the mouth), the seal may change if the head–neck is moved and it cannot be inserted if the inter-dental distance is less that 20 mm (maximal od of ILMA). In theory, the rigid tube might be more traumatic to teeth and a higher incidence–different type of sore throat. Trauma of teeth caused by biting may be prevented by use of a thick roll of gauze swabs. This also facilitates stabilization of the ILMA in the mouth.

The ILMA offers several advantages for difficult airway management. First, the difficulty in viewing the larynx which often underlies failed laryngoscopic intubation is probably irrelevant to ILMA placement and subsequent intubation. Placement of the standard LMA is probably independent of factors used to predict[18 19] or score[20] difficult intubation and the success rate of LMA placement in the abnormal airway has been reported at 97–100%.[10–12] Our data suggest that ILMA placement is similarly easy, although numbers are limited. The finding that tracheal intubation was easier in the abnormal airway requires further assessment, but it is possible that the high anterior larynx associated with Cormack and Lehane III and IV[21] may facilitate better alignment of the ILMA tube and glottic aperture. Second, the ILMA allows ventilation to be continued during intubation attempts, minimizing the risk of hypoxaemia and allowing an unhurried approach to securing the airway. Third, no movement of the cervical spine is required with the ILMA and this may be important for patients with cervical spine pathologies as placement can be accomplished in the neutral position. Fourth, placement of the ILMA and subsequent intubation are blind techniques (although a fibreoptic scope can be used to place the TT) thus accessory equipment is not required and placement unaffected by heavy secretions or blood which might impair fibreoptic techniques. Finally, placement does not require the practitioner to be above the patient's head.

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The intubating laryngeal mask airway: an initial assessment of performance†

A. KAPILA, E. V. ADDY, C. VERGHESE AND A. I. J. BRAIN

Summary

A new prototype of the laryngeal mask airway (LMA), the intubating laryngeal mask airway (ILMA), was used to facilitate tracheal intubation in 100 fasted patients presenting for elective surgery. Alignment of the ILMA with the larynx was assessed fibreoptically before intubation without the investigator performing the intubation being aware of the view score. Ease of intubation correlated with the view obtained and with the degree of manipulation of the ILMA needed to achieve tracheal intubation. Intubation was successful in 93 patients. Of the seven intubation failures, five occurred in the first 20 patients. Conventional connection to the breathing system and ventilation of the lungs of the patients were possible throughout the intubation procedure. (*Br. J. Anaesth.* 1997; **79**: 710–713).

Key words

Equipment, masks anaesthesia. Intubation tracheal. Intubation tracheal, technique.

The laryngeal mask airway (LMA) represents a major advancement in airway management.[1] In addition, it has been used to facilitate tracheal intubation by a variety of methods.[2-9] An early prototype of the laryngeal mask airway was used for intubation in a patient known to present with a difficult tracheal intubation.[10] We describe a new prototype, the intubating laryngeal mask airway (ILMA),[11] and a preliminary assessment of its performance in aiding tracheal intubation in fasted surgical patients.

Patients and methods

The ILMA (fig. 1) incorporates a standard LMA cuff in sizes 3, 4 or 5 and a metal airway tube and handle. The latter allows manipulation of the device within the patient's airway. The airway tube has a wider internal diameter (1.3 *vs* 0.9 cm) and is shorter 14.5 *vs* 20 cm) than the standard LMA tube (size 3 or 4). In addition, there is a silicon rubber bite block surrounding the upper part of the stem. The ILMA admits up to a 9.0 mm cuffed tracheal tube.

After obtaining Ethics Committee approval, informed consent was obtained from ASA I and II adult patients presenting on elective surgical lists. Patients were excluded if they had a history of active gastro-oesophageal reflux, severe respiratory disease or inadequate fasting. After i.v. induction of anaesthesia with fentanyl 1 μg kg^{-1} and a sleep dose of propofol, neuromuscular block was produced with atracurium 0.6 mg kg^{-1}. The lungs were pre-oxygenated and patients were monitored with ECG, capnography, pulse oximetry and a peripheral nerve stimulator. Patients' lungs were gently ventilated manually by face mask and after ablation of the train-of-four response to peripheral nerve stimulation an ILMA of appropriate size to patient weight was introduced (usually a size 4 for females and size 4 or 5 for males). The ILMA was preloaded with a 7 or 8 mm cuffed tracheal tube (TT) (Portex Ltd, Hythe, Kent, UK) with the cuff of the TT tube inflated within the stem of the ILMA to ensure an airtight seal. Before insertion, the cuff of the ILMA was deflated using a cuff deflating device (Intavent Orthofix Ltd, Maidenhead, Berks, UK) to ensure maximal extraction of air yet retaining a smooth cuff profile; the dorsal surface was lubricated with KY jelly (Johnson and Johnson Ltd, Maidenhead, UK). When the ILMA had been inserted by passing the device along the posterior pharyngeal wall, conventional connection of the TT tube to an anaesthetic breathing system and ventilation of the patients' lungs was attempted (fig. 1). Successful placement/ventilatory ability was judged by chest wall movement and capnography (maintain $P\text{E}'_{\text{CO}_2}$ within normal range) during gentle manually assisted ventilation. Inhalation anaesthesia with nitrous oxide and enflurane in oxygen was introduced at this stage.

Alignment of the ILMA with the larynx was assessed by an independent observer using a fibreoptic intubating laryngoscope, (Olympus LF-2, Keymed Ltd, Keymed House, Southend-on-Sea, UK) which was passed through the diaphragm of the tracheal tube connector (Intersurgical, Wokingham, UK) until the tip was lying just inside the ILMA

A. KAPILA, BSC, MB, BS, FRCA, C. VERGHESE, MB, BS, FRCA, Royal Berkshire Hospital, Reading, Berkshire RG1 5AN. E. V. ADDY, BSC, MB, BS, MRCP, FRCA, Oxford Radcliffe NHS Trust, Oxford. A. I. J. BRAIN, MA, LMSSA, FFARCS(I), Royal Berkshire Hospital and Institute of Laryngology, University of London, London.
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Correspondence to A. K.

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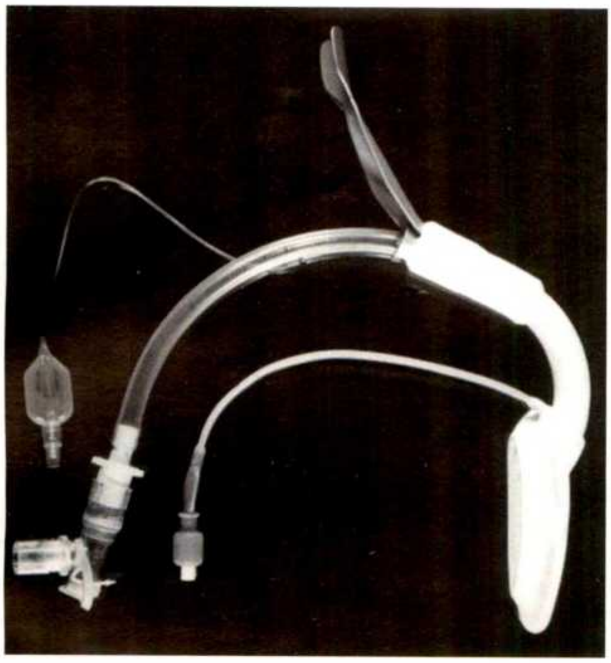

Figure 1 Intubating laryngeal mask airway showing a TT tube with diaphragm connector (for fibreoptic sight and assessment of laryngeal position) inserted into the metal stem of the ILMA. Inflation of the TT tube cuff within the ILMA stem and connection of the TT tube connector to the breathing system enables ventilation of the lungs.

Table 1 Fibreoptic view scoring system

Fibreoptic view	Score
Full view of cords	1
Partial view of cords, including arytenoids	2
Epiglottis only	3
Other (e.g. LMA cuff, pharynx)	4

grill. The view obtained was then graded according to a scoring system (table 1).

Without movement of the patient's head and neck from the "sniffing position", obtained with one pillow, TT tube advancement (by either A. K. or E. V. A.) was attempted using one or more of the following methods: (a) without movement of the ILMA (neutral), (b) pulling back of the metal handle of the ILMA towards the intubator (extension) or (c) pushing the metal handle of the ILMA away from the intubator (flexion). Manoeuvres (b) and (c) achieve a rotatory movement of the ILMA in the sagittal axis within the patient's airway and affect alignment of the mask with the larynx. Ease of intubation was assessed by recording the number of attempts required to intubate the patient's trachea and the final position of the ILMA at the time of TT intubation was noted. Successful intubation was confirmed by capnography during manually assisted ventilation. Failure to intubate was defined as inability to place the TT tube successfully after all three manoeuvres had been attempted. The ILMA was left *in situ* for the duration of the case with the cuff deflated.

Results

We have used the ILMA in 100 patients (30 male). Mean age was 50.1 (range 22–87) yr and mean weight 68.7 (range 40–107) yr. Anaesthesia was uneventful in all patients. Placement of the ILMA and adequate ventilation were achieved at the first attempt in all patients. The trachea was intubated successfully in 93 patients, 72 at the first attempt. Of the 28 patients requiring more than one attempt at TT intubation, difficulties with tube advancement resulted from two causes: either TT tube passage was obstructed (this occurred in 25 patients of which 21 patients were intubated successfully after manipulation (table 2)), or the tube passed into the oesophagus (this occurred in three cases and was recognized by the absence of chest wall movement and the use of capnography). Of the seven failed intubations, five occurred in the first 20 patients. Of the 93 patients with a view score of 1 or 2, there was a 95% success rate at tracheal intubation. Of the five patients with a view score of 3, there were four successful intubations and one failure. Of the two patients with a view score of 4, there was one successful and one failed intubation (table 3). The first was caused by the ILMA being inserted too far, resulting in oesophageal intubation (with only the oesophagus being visible on fibreoptic examination); tracheal intubation was achieved when the ILMA was withdrawn slightly. In the second, the ILMA tip had folded forwards, obstructing tracheal tube advancement and was an intubation failure. This patient was one of the failures occurring after the first 20 patients (late failure). The other late failure was a patient who had a view score of 2 after ILMA insertion, but attempts with all three manipulations of the ILMA still resulted in oesophageal intubation. Removal of one pillow and a less exaggerated "sniffing position" enabled easy intubation subsequently; however, this patient was classified as an intubation failure as the fibreoptic view score was known to the intubator.

Table 2 Attempts at tracheal intubation

Attempts at intubation	No.of patients
1 (no manipulation)	72 (72%)
2 or more (manipulation)	21 (21%)
Failed	7 (7%)

Table 3 Attempts at intubation, classified by fibreoptic view score

	View score			
Attempts at intubation	1	2	3	4
1	47 (85%)	23 (60%)	2 (40%)	0 (0%)
2 or more	6 (11%)	12 (32%)	2 (40%)	1 (50%)
Failed	2 (4%)	3 (8%)	1 (20%)	1 (50%)
	55	38	5	2

As the fibreoptic view score deteriorated, more attempts were required to achieve intubation. When success was achieved in patients with a view score of 1, 2, 3 or 4, six of 53 (12%), 12 of 35 (34%), two of four (50%) and one of one (100%) patients, respectively, required two or more attempts at intubation.

In achieving tracheal intubation in those patients with a view score of 1, the ILMA was manipulated

Table 4 Manipulation of the ILMA in successful intubations according to view score

	View score			
Manipulation	1	2	3	4
Neutral (a)	16	7	0	0
Extension (b)	18	5	2	0
Flexion (c)	19	23	2	1

in approximately equal degree between the manoeuvres (a)–(c) (intubation was successful in 16 patients in the neutral position, in 18 patients after extension and in 19 patients after flexion manoeuvres of the ILMA). As the alignment of the larynx with the ILMA deteriorated (i.e. view scores 2–4), the final position of the ILMA was predominantly flexion (26 patients), rather than neutral (seven patients) or extension (seven patients) (table 4).

Discussion

We have made a preliminary assessment of the performance of a new prototype of the laryngeal mask airway, the ILMA. After insertion of the ILMA in anaesthetized patients, alignment of the ILMA with the larynx was assessed fibrescopically by an independent observer before the attempted passage of a TT tube. A scoring system for the fibreoptic view obtained was based on the direct laryngoscopy grading of Cormack and Lehane[12] and differs from that described by Brimacombe and Berry.[13] It separates view of the larynx from function of the laryngeal mask and is familiar to anaesthetists. Tracheal intubation in 93 of 100 patients was successful. The majority of patients (93) had a view score of 1 or 2 and the trachea was intubated with a success rate of 95%. Of the seven failed intubations, five occurred in the first 20 patients (four with a view score of 1 or 2), demonstrating the presence of a learning curve in acquiring expertise in the use of this prototype of the ILMA. In the five patients with a view score of 3 (only epiglottis visible), four successfully underwent intubation. The degree of device manipulation required to achieve tracheal intubation was related inversely to the view score or alignment with the larynx.

The laryngeal mask airway has been used to facilitate tracheal intubation by a variety of methods.[2–8] It has been recommended as a conduit for fibreoptic intubation for training purposes[14] and for the management of some patients with difficult airways.[15] The salient feature is the possibility of maintaining an airway and oxygenation of the patient throughout the intubation procedure. However, the standard LMA only admits up to a 6.0 mm cuffed tracheal tube. In addition, the cuff of such a tube will not reliably come to lie in the trachea below the vocal cords[16] because of the length of the stem of the LMA. Attempts to overcome these problems have involved cutting and altering the standard laryngeal mask airway.[14 17] The design of the ILMA with its shorter and wider airway tube attempts to overcome these problems and admit up to a 9.0 mm cuffed TT tube.

In this study patients were paralysed (only after it was confirmed that manual ventilation using a face mask was possible), however if neuromuscular blocking agents were not used it may be that in those patients requiring more than one attempt at TT intubation this degree of airway manipulation could provoke laryngeal spasm. In a case of difficult intubation where neuromuscular blocking agents are usually avoided there are two options with this device. First, the ILMA may be inserted and intubation achieved with the patient awake using topical anaesthesia (personal communication L. Loh, Oxford and D. R. Uncles, Worthing). Second, the ILMA may be inserted after induction of anaesthesia and adequate ventilation of the patient's lungs confirmed before administration of a neuromuscular blocker.

The ILMA as an intubating aid may be criticized for being a "blind-on-blind" technique (i.e. both the ILMA and TT tube are inserted without direct sight of the larynx). However, other blind techniques for intubation have been described[18 19] and blind intubation through the standard LMA has been demonstrated successfully.[3] Moreover, fibrescopy may be performed either before or during the intubation attempt if the equipment is available. With the ILMA, manipulation of the rigid tube and handle is transmitted directly to the inflatable cuff, altering its position within the patient's airway, unlike the standard LMA or more particularly the reinforced LMA. We believe that this manipulation enabling alignment of the ILMA with the laryngeal inlet to facilitate tracheal intubation while being able to ventilate the patient's lungs throughout the procedure may represent a valuable advance over current intubation aids.

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Skin vasomotor reflex induced by laryngoscopy: comparison of the McCoy and Macintosh blades

O. SHIMODA, Y. IKUTA, S. ISAYAMA, M. SAKAMOTO AND H. TERASAKI

Summary

We studied 22 female patients (ASA I or II) to investigate if laryngoscopy and intubation induced the skin vasomotor reflex (SVmR), and to compare the effects of the McCoy and Macintosh blades on the SVmR. Anaesthesia was induced with fentanyl, midazolam, vecuronium and nitrous oxide. In 11 patients, the vocal cords were seen for 3 s with the McCoy blade. Two minutes later, laryngoscopy was performed with the Macintosh blade and the trachea was intubated. In the other 11 patients, the first and second laryngoscopies, respectively, were performed with the Macintosh and McCoy blades. Laryngoscopy alone and intubation with laryngoscopy significantly reduced skin blood flow in the ring finger of all patients ($P<0.01$), indicating that both procedures provoked the SVmR. The magnitude of the SVmR and haemodynamic changes did not differ significantly between the two groups. (*Br. J. Anaesth.* 1997; **79**: 714–718).

Key words
Anaesthetic technique, laryngoscopy. Larynx, laryngoscopy. Measurement techniques, flowmetry. Skin, blood flow.

Although many investigators have documented a relationship between detrimental circulatory responses and intubation with direct laryngoscopy,[1–7] there have been few reports of changes in skin blood flow during these procedures. The recent development of the laser Doppler (LD) flowmeter provides a useful tool for observation of skin vasomotion. LD skin blood flow (LD-SBF) is composed of three components: cardiac, basic and reflex waves.[8] The reflex wave that follows an inspiratory gasp or various other somatosensory stimuli manifests as a transient marked reduction in LD-SBF,[8–10] and this has been termed the skin vasomotor reflex (SVmR).[9] We found recently that various surgical stimuli provoked the SVmR, even under general anaesthesia. As the SVmR is transferred to skin vessels via sympathetic nerves,[11–13] it would represent the magnitude of the stress response as a somato-sympathetic reflex when the SVmR is induced by somatosensory stimulation. The main purpose of this study was to investigate if laryngoscopy and intubation induce the SVmR as a stress response.

McCoy, Mirakhur and McCloskey reported that circulatory responses to laryngoscopy were less marked with the use of the McCoy blade compared with the Macintosh blade,[14] suggesting that a decreased stress response results from less force being necessary with the McCoy blade during laryngoscopy.[15] The second purpose of the study was to compare the McCoy and Macintosh blades regarding the magnitude of the SVmR and the circulatory responses during laryngoscopy and intubation.

Patients and methods

The study was approved by the Institutional Review Board of our hospital, and written informed consent was obtained from all patients. We studied 22 patients undergoing elective gynaecological surgery under general anaesthesia with tracheal intubation. All patients were ASA I or II. Patients were allocated randomly to a McCoy–Macintosh (McC–Mac) ($n=11$) or Macintosh–McCoy (Mac–McC) ($n=11$) group. Patients with signs of autonomic dysfunction or cardiovascular disease detected by routine clinical laboratory tests and preanaesthetic interview were excluded because the SVmR is suppressed significantly in patients with autonomic neuropathy.[9 10 16] No patient was receiving chronic medication, was obese (body mass index more than 26 kg m^{-2}) or had an anticipatory difficult airway.

Atropine 0.5 mg i.m. and either hydroxyzine 1 mg kg^{-1} or midazolam 0.08 mg kg^{-1} were administered to patients 30 min before they entered the operating room. In the operating room, the lead CM5 electrocardiogram (ECG) and pulse oximeter were monitored using a Datex AS/3 anaesthesia monitor (Helsinki, Finland). Heart rate (HR) was measured by the moving average method, which used 4 beats if HR was less than 99 beat min^{-1} and 8 beats if HR was equal to or more than 100 beat min^{-1}. Tonometric arterial pressure (TAP), which has been reported to have an excellent correlation with invasive arterial pressure,[17] was measured by the

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OSAMU SHIMODA, MD, SAKIKO ISAYAMA, MD, HIDENORI TERASAKI, MD, Department of Anesthesiology, Kumamoto University School of Medicine, 1-1-1 Honjo, Kumamoto 860, Japan. YOSHIHIRO IKUTA, MD, MASAKATSU SAKAMOTO, MD, Surgical Centre, Kumamoto University Hospital, 1-1-1 Honjo, Kumamoto 860, Japan. Accepted for publication: July 22, 1997.
Correspondence to O. S.

Nippon Colin BP-508-type S tonometer (Komaki, Japan). The tonometer sensor was attached to the left wrist over the radial artery and calibrated at intervals of 2.5 min by an oscillometric cuff attached to the right upper arm. Arterial pressure was monitored continuously and recorded by a heat pen recorder. Ambient temperature was maintained at 25–26 °C.

An i.v. cannula was inserted into the median antecubital vein of the right arm for infusion of Ringer's lactate solution and drug administration. General anaesthesia was induced with fentanyl 3 μg kg^{-1} i.v. and midazolam 0.1 mg kg^{-1} i.v. After loss of consciousness, vecuronium 0.1 mg kg^{-1} was administered. Subsequently the patient's lungs were ventilated via a face mask with 50% nitrous oxide in oxygen through a semi-closed anaesthesia system. End-tidal concentrations of carbon dioxide and nitrous oxide, obtained from the Y-piece of the anaesthesia system, were monitored by the AS/3 system. Neuromuscular block was monitored by transcutaneous electrical stimulation of the right ulnar nerve (Innervator, Fisher and Paykel, Auckland, New Zealand).

In the McC–Mac group, laryngoscopy was performed with the McCoy blade (size 3) after complete neuromuscular block was achieved (laryngoscopy-1). The standard manner, including "levering"[18] of the McCoy blade, was used. After a clear view of the vocal cords was obtained (grade I view defined by Cormack and Lehane) for 3 s, laryngoscopy was discontinued. The patient's lungs were ventilated again via the face mask with 50% nitrous oxide in oxygen for 2 min. Laryngoscopy was then performed with the Macintosh blade (size 3) and the trachea was intubated immediately (intubation with laryngoscopy-2). In the Mac–McC group, the same procedures were performed but the laryngoscopies were performed with the Macintosh and McCoy blades, respectively. We changed the blade with each laryngoscopy to reduce the bias of the anaesthetist concerning the blades. One of two trained anaesthetists who were familiar with each blade was allocated randomly to the groups. They were blinded to the results of skin blood flow (described later) and changes in arterial pressure and heart rate.

MONITORING LASER DOPPLER SKIN BLOOD FLOW (LD-SBF)

For monitoring LD-SBF we used an LD flowmeter (ALF 2100, Advance, Tokyo). A plate-type probe was attached to the palmar side of the left ring fingertip by double-sided adhesive disk. Details of the LD flowmeter have been described previously.[8–10] The fingertip has rich arteriovenous anastomoses innervated with sympathetic fibres.[10 19] We selected the ring finger to reduce artefacts of the tonometer sensor on the LD-SBF wave because blood flow to the ring finger is supplied predominantly by the ulnar artery. The output signal of the LD flowmeter was recorded on a heat pen recorder at a time constant of 1.0 s.

Ambient temperature, finger temperature, mental strain and the condition of the skin contacting the probe can influence vasomotion.[10 19] Therefore, before induction of anaesthesia, the SVmR was tested by an inspiratory gasp to detect any subclinical vasomotor disorder or probe factor.[8–10] Patients lacking the SVmR were excluded from further study. After induction of anaesthesia, a marked reduction in the LD-SBF following each procedure was recognized as the SVmR (fig. 1).[8–10]

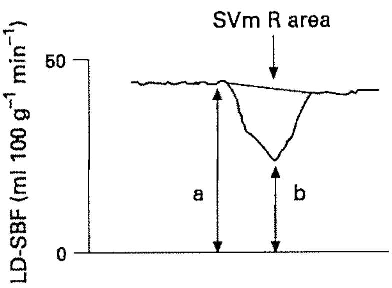

Figure 1 Measurement of the skin vasomotor reflex (SVmR). a=Laser-Doppler skin blood flow (LD-SBF) immediately before laryngoscopy; b=minimal LD-SBF during laryngoscopy or tracheal intubation. The reduction ratio of SVmR (SVmR-RR) was calculated by the equation described in the text The area over the LD-SBF wave and under the tangent line drawn between the drop point and recovery point was measured as SVmR area.

The LD-SBF wave recorded on a heat pen recorder was scanned by a ScanJet IIc with DeskScan II software (Hewlett Packard, Palo Alto, CA, USA) and saved in the TIFF format. Analysis of the magnitude of the SVmR was performed on a Power Macintosh 8500/120 computer (Apple, Cupertino, CA, USA) using the public domain NIH image program (developed at the US National Institutes of Health and available from the Internet by anonymous FTP from zippy.nimh.nih.gov or on floppy disk from the National Technical Information Service, Springfield, VA, part number PB95-500195GEI). We used two indices to quantitatively evaluate the magnitude of the SVmR. The reduction ratio in the SVmR (SVmR-RR) was calculated using the following equation (fig. 1)[9 10 16]:

$$\text{SVmR-RR} = 1 - b / a$$

where a=LD-SBF immediately before laryngoscopy and b=minimal LD-SBF during laryngoscopy or tracheal intubation. The area over the LD-SBF wave and under a tangent line drawn between the drop point and recovery point (fig. 1) was measured as SVmR area by the unit of pixel.

DATA ANALYSIS

Mean arterial pressure (MAP) was calculated as diastolic arterial pressure and one-third pulse pressure. The change in MAP was measured as the difference between MAP recorded before laryngoscopy-1 and maximum MAP in the period during laryngoscopy-1 to 2 min after this. In a similar manner, the change in MAP during intubation with laryngoscopy-2 was calculated using the arterial pressure value from before laryngoscopy-2 to 2 min after intubation. The change in HR in laryngoscopy-1 was determined as the difference between HR recorded before laryngoscopy-1 and maximum

HR during laryngoscopy-1 to 2 min after this. The change in HR in intubation with laryngoscopy-2 was calculated similarly.

Results are presented as mean (SD). Haemodynamic data within each group were analysed using a repeated measures analysis of variance, and differences between groups were analysed using the Student's *t* test. Changes in LD-SBF, SVmR-RR and SVmR area were assessed by the Wilcoxon signed rank test within each group, and the Mann–Whitney *U* test between groups. $P<0.05$ was considered significant.

Results

An inspiratory gasp provoked the SVmR in all patients before induction of anaesthesia; therefore, none was excluded. Patient age, weight and body mass index in the McC–Mac group were 34.2 (range 21–47) yr, 54.9 (SD 10.3) kg and 22.3 (2.7), respectively. Those in the Mac–McC group were 34.5 (26–50) yr, 55.3 (6.9) kg and 22.9 (2.6). There were no significant differences between the groups in patient characteristics. No patient had a difficult airway. A clear view of the vocal cords (grade I view defined by Cormack and Lehane) was obtained with both the Macintosh and McCoy blades in each patient.

Figure 2 shows simultaneous recording of tonometry arterial pressure (TAP) and LD-SBF level of representative patients from the McC–Mac group (top) and the Mac–McC group (bottom). Table 1 lists the changes in LD-SBF level. The LD-SBF level increased after induction of anaesthesia in both groups. Laryngoscopy-1 and intubation with laryngoscopy-2 procedures significantly reduced the LD-SBF level in both groups ($P<0.01$). The LD-SBF level at 1 min after each procedure recovered to the level observed immediately before the procedure. There were no significant differences between the groups regarding changes in LD-SBF level.

MAGNITUDE OF THE SVMR AND HAEMODYNAMIC RESPONSES

There were no significant differences in SVmR-RR between the two groups (table 2). In each group, the SVmR-RR of laryngoscopy-1 also did not differ from that of intubation with laryngoscopy-2. There was no significant difference between the groups in

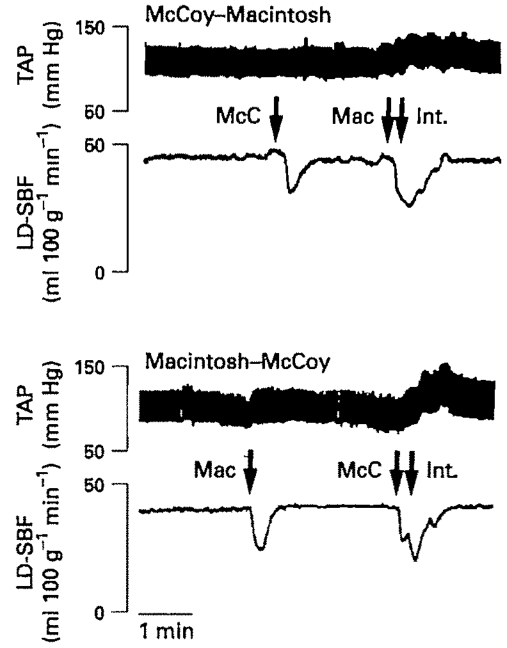

Figure 2 Representative records illustrating the relationship between tonometry arterial pressure (TAP) and skin blood flow on the laser-Doppler flowmeter (LD-SBF) (top: patient in the McCoy–Macintosh group; bottom: patient in the Macintosh–McCoy group). The arrows with "McC" and "Mac" indicate laryngoscopy with the McCoy and Macintosh blades, respectively. Int. = tracheal intubation.

Table 1 Mean (SD) changes in laser-Doppler skin blood flow (LD-SBF) (ml 100 g^{-1} min $^{-1}$). $n=11$ patients in each group. $^{**}P<0.01$ compared with previous time point within a group

	McCoy–Macintosh	Macintosh–McCoy
Baseline	15.1 (11.6)	16.0 (9.4)
Before laryngoscopy-1	38.2 (10.9)**	42.7 (10.5)**
Minimum during laryngoscopy-1	17.2 (11.2)**	25.9 (13.2)**
1 min after laryngoscopy-1	36.1 (9.3)**	40.1 (9.4)**
Before laryngoscopy-2	38.4 (10.2)	44.8 (9.2)
Minimum during intubation	11.0 (9.8)**	16.2 (11.2)**
1 min after intubation	38.9 (11.2)**	44.2 (9.6)**

Table 2 Changes in skin vasomotor reflex (SVmR) and haemodynamic data (mean SD)). $n=11$ patients in each group. SVmR-RR=reduction ratio of skin vasomotor reflex. $^{*}P<0.05$, $^{**}P<0.01$, laryngoscopy alone *vs* larnygoscopy and intubation within a group

	McCoy–Macintosh		Macintosh–McCoy	
	Laryngoscopy-1	Intubation with laryngoscopy-2	Laryngoscopy-1	Intubation with laryngoscopy-2
SVmR-RR	0.57 (0.20)	0.72 (0.18)	0.51 (0.29)	0.64 (0.25)
SVmR area (pixel)	450 (276)	903 (515)*	421 (308)	751 (396)**
Changes in HR (beat min^{-1})	0.9 (3.4)	12.4 (9.8)**	0.9 (3.7)	9.1 (5.1)**
Changes in MAP (mm Hg)	7.4 (7.3)	17.3 (12.2)*	4.8 (3.4)	14.8 (10.2)*

SVmR area; however, SVmR area in intubation with laryngoscopy-2 was significantly greater than that in laryngoscopy-1 within each group ($P=0.01$ in the McC–Mac group; $P=0.005$ in the Mac–McC group). HR and MAP did not change during laryngoscopy-1, whereas intubation with laryngoscopy-2 significantly increased both HR ($P=0.006$ in the McC–Mac group; $P=0.008$ in the Mac–McC group) and MAP ($P=0.04$ in the McC–Mac group; $P=0.03$ in the Mac–McC group). However, haemodynamic changes were not significantly different between groups.

Discussion

We have demonstrated that both laryngoscopy and intubation provoked the skin vasomotor reflex (SVmR), nociceptive stimulation by intubation with laryngoscopy had a larger magnitude than that by laryngoscopy alone and the magnitude of nociception caused by laryngoscopy, which was measured by the SVmR, did not differ whether the Macintosh or McCoy blade was used.

The SVmR involves complex mechanisms, that is afferent, central and efferent pathways.[9–13] An inspiratory gasp and various sensory stimuli are representative afferent inputs for the SVmR. During laryngoscopy and intubation, nociceptive signals are generated by elevation of the epiglottis with the laryngoscope and by insertion of the tube into the trachea. The signals are conducted to the brain through the glossopharyngeal nerve and the vagus. The central polysynaptic pathways of the SVmR have not yet been clarified. The pressor response to laryngoscopy and intubation is mediated via sympathetic nerves.[20–22] The efferent pathway of the SVmR caused by any afferent stimulus has also been reported to be composed of sympathetic nerve fibres.[9–13]

The anaesthesia techniques among the studies of circulatory responses to laryngoscopy and intubation have varied widely.[1–7,20–22] As changes in HR and MAP in our study did not differ markedly from the haemodynamic changes in non-treated groups in previous reports,[1–7] our anaesthetic technique was adequate for tracheal intubation. We found recently that laryngoscopy and intubation provoked the SVmR during induction of anaesthesia with both nitrous oxide–sevoflurane and fentanyl–propofol (unpublished observation). Sympathetic vasomotor activity may exert potent control of vascular resistance in the skin and skin tissues which serve as potentially major targets for powerful sympathetic homeostatic reflexes.[23] Sympathetic discharge patterns recorded simultaneously from different skin nerves show striking similarities.[24] Our findings suggest that the SVmR contributes, at least in part, to the haemodynamic responses during laryngoscopy and intubation. There are few reports of the SVmR during general anaesthesia. Further studies are necessary to clarify if there is an intimate relationship between the SVmR and haemodynamic responses during laryngoscopy and intubation.

The SVmR is an indirect method of assessment of the sympathetically mediated reflex. It has not yet been confirmed if a linear, quantitative correlation exists between the magnitude of the SVmR and skin sympathetic nerve activity. However, the relationship between the SVmR-RR induced by transcutaneous electrical stimulation of the ulnar nerve and the current intensity of the stimulus showed a significant correlation during nitrous oxide–sevoflurane anaesthesia (unpublished observation). Evaluation of the SVmR may have the potential to be a non-invasive indicator of nociception during general anaesthesia.

We found that combined laryngoscopy and intubation provided larger nociceptive stimulation compared with laryngoscopy alone. The durations of the two procedures should not account for the difference because the elimination half-lives of fentanyl and midazolam are reported to be 3.6 h[25] and 3.8 h,[26] respectively. Stoelting reported that prolonged laryngoscopy increased mean arterial pressure with time during the first 45 s.[27] This report and our findings suggest that the duration of nociceptive stimulation itself plays an important role in the magnitude of SVmR area and haemodynamic changes during laryngoscopy and intubation.

McCoy and colleagues demonstrated that the circulatory responses to laryngoscopy were less marked with the McCoy blade compared with the Macintosh blade.[14,15] In our study there were no significant differences in the magnitude of the SVmR and haemodynamic changes induced by the use of either blade. To expose the larynx, the tip of the blade is inserted into the epiglottic vallecula and moved up towards the mandible. These procedures are common to each blade. Regardless of the blade style, a 3-s view of the larynx caused the SVmR. Cook and Turky reported that the McCoy blade in the neutral position provided a poorer view of the larynx and needed "levering" to obtain the view similar to that provided by the Macintosh blade.[28] This report and our findings suggest that the magnitude of nociception caused by elevation of the epiglottis itself does not differ between the two blades for patients with a normal body size and anatomical structure of the upper airway.

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Effect of felodipine on renal function and vasoactive hormones in infrarenal aortic surgery

L. DE LASSON, H. E. HANSEN, B. JUHL, W. P. PAASKE AND E. B. PEDERSEN

Summary

We have examined the possible renoprotective effect of felodipine 5 mg orally, given daily for 5 days before operation, in 29 patients undergoing elective infrarenal aortic surgery in a randomized, blinded and placebo-controlled study. Effective renal plasma flow (ERPF), glomerular filtration rate (GFR), urine output, fractional sodium clearance and plasma concentrations of angiotensin II, aldosterone, arginine vasopressin and atrial natriuretic peptide did not differ between the felodipine and placebo groups. ERPF and GFR were not reduced after operation in the placebo group. In the felodipine group, GFR was higher 24 h after operation compared with before operation. We conclude that increased GFR in the felodipine group, measured 24 h after operation, may indicate a beneficial effect of felodipine but in the present context this was not clinically important. Felodipine had no significant effect on vasoactive hormones. (*Br. J. Anaesth.* 1997; **79**: 719–725).

Key words
Calcium channel block, felodipine. Kidney, blood flow. Surgery, vascular. Hormones, vasoactive.

It is not known why effective renal plasma flow (ERPF) and glomerular filtration rate (GFR) decrease after cross-clamping of the infrarenal aorta[1] [2] or why reduced renal blood flow is associated with decreased postoperative creatinine clearance.[3] The cause of this renal impairment is probably multifactorial.

Calcium antagonists cause vasodilatation at raised tone in afferent renal arterioles and ameliorate experimental renal ischaemia.[4] Felodipine is a dihydropyridine calcium antagonist, characterized by high vascular selectivity, which causes a reduction in systemic vascular resistance, and has no adverse effects on myocardial contractility or conduction.

In this prospective, randomized, placebo-controlled study, we have examined if treatment with felodipine for 5 days before operation influenced ERPF, GFR, fractional excretion of sodium and potassium, osmolar clearance or vasoactive hormones in elective surgery for infrarenal atherosclerosis.

Patients and methods

We studied 29 patients with aorto-iliac occlusive arterial disease undergoing elective aorto-biliac or aorto-bifemoral graft implantation. The study was approved by the Danish National Health Board and the local Ethics Committee, and all patients gave written informed consent. One of the authors (L. de L.) anaesthetized all patients.

Patients were invited to participate in the study if kidney function was normal after diethyltriamine-pentaacetic acid (DTPA) renography. Exclusion criteria were: age more than 70 yr; myocardial infarction within the past year; cardiovascular symptoms or receiving medications; unstable angina or stable angina with congestive heart failure; symptomatic cerebrovascular disease; diabetes mellitus; diastolic arterial pressure ≥100 mm Hg; cardiac valvular stenosis with haemodynamic implications; systemic therapy with bronchodilators or steroids; or treatment with a calcium antagonist or an angiotensin converting enzyme inhibitor.

Patients were excluded during the study if they experienced postoperative pain requiring replacement of extradural catheter, loss of more than 50% of estimated blood volume or there were technical failures during sampling.

FELODIPINE TREATMENT AND SIDE EFFECTS

The randomization and preparation of felodipine extended release tablets (5 mg) and placebo were undertaken by Astra AB, Sweden. This dose was chosen because patients were normotensive. Felodipine treatment was started 5 days before operation, after a clearance test. The day before operation, patients were asked if they had any complaints relating to felodipine treatment including, ankle oedema, headache, flushing, palpitations, dizziness or tiredness. All patients received their last felodipine dose 1.5–2.5 h before anaesthesia.

L. DE LASSON*, MD, PHD, FRCA, B. JUHL, MD, DMSCI (Department of Anaesthesiology), H. E HANSEN, MD, DMSCI (Department of Nephrology); W. P. PAASKE, MD, DMSCI (Department of Cardiothoracic and Vascular Surgery); E. B PEDERSEN, MD, DMSCI (Research Laboratory for Nephrology and Hypertension), Aarhus University Hospital, Skejby Sygehus, DK-8200 Aarhus N, Denmark. Accepted for publication: July 15, 1997.

Correspondence to L. De L.

RENAL HAEMODYNAMICS, HORMONES AND ELECTROLYTES

ERPF and GFR were measured before treatment with felodipine or placebo and twice after operation (when patients were haemodynamically stable, 1 h after operation and 24 h after operation). On these three occasions, plasma concentrations of angiotensin II, aldosterone, arginine vasopressin (AVP) and atrial natriuretic peptide (ANP) were measured. On the same three occasions, plasma concentrations of electrolytes were analysed for calculation of clearances of sodium, potassium and water, and osmolality was also measured. Plasma concentrations of felodipine were measured 1 and 24 h after operation.

ANAESTHESIA AND ANALGESIA

Premedication comprised diazepam 10–15 mg orally, 1 h before anaesthesia. An extradural catheter was inserted at T10–11 or one segment above, and 0.5% plain bupivacaine 6–10 ml was administered as a bolus followed by an infusion of 5 ml h^{-1}. General anaesthesia was induced with midazolam 2.5–5 mg, fentanyl 3–5 $\mu g\ kg^{-1}$ and thiopentone 50–250 mg. The trachea was intubated after administration of pancuronium 1 mg and suxamethonium 75–100 mg i.v. A bolus dose of pancuronium 6–8 mg was given to achieve neuromuscular block. Anaesthesia was maintained with 0.4–1.0% halothane. Signs of patient discomfort during surgery (increased heart rate or arterial pressure, dilated pupils or sweating) were treated with extradural bupivacaine 3 ml at incision and later with alfentanil 0.5 mg i.v. Hypotension was treated with a bolus dose of ephedrine 2–5 mg or noradrenaline 2–5 μg (if systemic vascular resistance was <800 dyn s cm^{-5}) while corrective measures were taken in terms of fluid infusion and adjustment of the level of anaesthesia. Dopamine 3 $\mu g\ kg^{-1}\ min^{-1}$ was administered after insertion of the pulmonary artery catheter until 06:00 the next morning. The trachea was extubated at the end of operation. After operation, extradural infusion continued with 0.17% plain bupivacaine 5–8 ml h^{-1} until midnight. In the intensive care unit, extradural morphine 3–4 mg was injected every 6–8 h. Diuretics were not administered during the study. Droperidol bolus doses of 1.25 mg were used as an antiemetic.

MONITORING

The ECG (leads II and V5) was monitored continuously. A 5-French thermodilution pulmonary artery catheter was inserted via the right internal jugular vein and a nasopharyngeal temperature probe, nasogastric tube and urinary bladder catheter inserted. During operation, systemic mean arterial pressure (MAP), pulmonary artery mean pressure (PAMP), heart rate (HR) and central venous pressure (CVP) were displayed continuously. Pulmonary artery wedge pressure (PAWP) and cardiac output were measured as required, and cardiac index (CI), stroke volume index (SVI) and systemic vascular resistance (SVR) were calculated. Haemodynamic observations were recorded five times during operation in all patients (before skin incision; before aortic cross-clamping; 5 min after clamping; at completion of vascular anastomoses; and at the end of operation) and at the same times as the postoperative clearance measurements.

Systemic arterial blood samples were analysed to ensure normocapnic ventilation and adequate oxygenation during operation.

FLUID TREATMENT

Before skin incision, fluid was administered to compensate for vasodilatation caused by extradural and general anaesthesia: Dextran 70, 60 mg ml^{-1} with isotonic sodium chloride 300–400 ml m^{-2} body surface area and an equal volume of isotonic saline. During operation, isotonic saline was infused to compensate for evaporation and third space loss: 600 ml m^{-2}, 400 ml m^{-2} and 200 ml m^{-2} in the first, second and third hours of operation, respectively. In addition, isotonic saline was given in a volume equivalent to the volume of urine produced during the previous hour of operation. Blood loss was compensated for by Dextran 70 up to a maximum dose of 1.5 g kg^{-1} and then human albumin was given. If packed cell volume was less than 0.28, SAG-M blood was transfused during and after operation.

After operation, crystalloid was infused at a rate of 60 ml $m^{-2}\ h^{-1}$ until the next morning at 06:00 and at 120 ml $m^{-2}\ h^{-1}$ thereafter. Human albumin was given if hypovolaemia occurred (hypotension at low PAWP and normal SVR).

LABORATORY ANALYSES

GFR and ERPF were measured by the constant infusion clearance method.[5] The reference substances were ^{125}I-iothalamate and ^{131}I-hippuran in the first 10 patients and ^{51}Cr-EDTA and ^{125}I-hippuran, respectively, in the other patients, because of administrative changes. The same method was used in each patient.

Angiotensin II was measured by radioimmunoassay using a modification of the method described by Kappelgaard, Nielsen and Giese.[6] The minimum detection level in plasma was 2 pmol $litre^{-1}$. Coefficients of variations were 12% (inter-assay) and 8% (intra-assay). Aldosterone was measured by a slight modification of a method described previously.[7] The minimum detection level was 42 pmol $litre^{-1}$. Coefficients of variation were 13% (inter-assay) and 9% (intra-assay). Atrial natriuretic peptide was measured by radioimmunoassay as described previously.[8] The minimum detection level in plasma was 0.5 pmol $litre^{-1}$. Coefficients of variation were 12% (inter-assay) and 10% (intra-assay). Arginine vasopressin was measured radioimmunologically by a slight modification of a method described previously.[9] The minimum detection level was 0.5 pmol $litre^{-1}$. Coefficients of variation were 13% (inter-assay) and 9%

(intra-assay). Plasma felodipine assays were conducted by Astra AB, Sweden. Clearance data were standardized to a body surface area of 1.73 m^2.

STATISTICAL ANALYSIS

In a previous study with similar patients,[11] there were 12 patients in each group and the SD for preoperative GFR was 17.5 ml min^{-1}. With a minimum relevant difference between means of 26.3 ml min^{-1}, $\alpha=0.05$ and $\beta=0.10$, the number of patients required in each group was calculated as nine. The Mann–Whitney and non-parametric two-way analysis of variance tests were used (significance level 0.05). Intra-group differences were examined by the Wilcoxon test (significance level 0.02). Unless otherwise specified, results are presented as median (interquartile ranges).

Results

There were 14 and 15 patients in the felodipine and placebo groups, respectively. Patients were not receiving cardiorespiratory drugs, except for one patient in the felodipine group who was treated with a diuretic for hypertension; this patient was not excluded.

Side effects of felodipine included headache in one patient, and another was exceptionally tired. One other patient reported palpitations, and one had flushing of the face and oedema of the ankles and fingers. In the placebo group, one patient confessed to all side effects. One patient complained of headache and one suffered from dizziness.

Table 1 Patient characteristics (values are median (range)). *Mean arterial pressure=1/3(systolic arterial pressure−diastolic arterial pressure)+diastolic arterial pressure

	Felodipine group	Placebo group
Sex (F/M)	5/6	9/3
Age (yr)	65 (46–69)	60 (47–68)
Height (m)	1.68 (1.52–1.80)	1.66 (1.54–1.77)
Weight (kg)	66 (53–79)	64.5 (54–82)
ASA II	11	12
Arterial pressure (mm Hg)*	95	94

Table 2 Duration of operation (OP), aortic cross-clamping time (ACC), and blood loss (values are median (interquartiles))

	Felodipine group	Placebo group
OP (min)	108 (99–158)	125 (116–150)
ACC (min)	19 (15–25)	20 (17–30)
Blood loss (ml)	1150 (550–1600)	1000 (544–1425)

Three patients were excluded from each group. In the felodipine group one patient developed influenza after randomization and the operation was cancelled; one patient lost excessive quantities of blood during operation; and the third patient had the extradural catheter replaced. In the placebo group, one patient lost excessive quantities of blood, one had replacement of the extradural catheter and one was excluded because of technical problems. Table 1 describes the 23 patients who completed the study. Age, weight and height in the two groups were well matched.

There were no major complications during or after operation. In the felodipine group, one patient developed sinus bradycardia on day 4 after operation. One patient developed a silent subendocardial infarction during the night before operation. She was discharged home 8 days after operation in good health. One patient in the placebo group had atrial fibrillation.

Duration of operation, aortic clamping time and intraoperative blood loss (table 2) were similar in the two groups. The number of patients who received bolus doses of ephedrine/noradrenaline was 6/4 in the felodipine group and 7/7 in the placebo group. Hypotension (SVR 430–813 dyn s cm^{-5}) on the night after operation was treated with infusion of noradrenaline in two patients in the felodipine group and in four patients in the placebo group. Two patients in the placebo group required infusion of noradrenaline during the last postoperative clearance measurement.

CENTRAL HAEMODYNAMICS

Mean preoperative arterial pressure (table 1) was unchanged in the felodipine group. There was no difference between the groups in central haemodynamic variables during operation (PAWP, CVP, HR, MAP, PAMP, CI, SVI and SVR). There was a time–treatment interaction for CVP and PAMP ($P=0.033$ and 0.035). CVP, PAMP and PAW are shown in figure 1 and HR, MAP and CI in table 3. We did not estimate intra-group differences as haemodynamic variations

Table 3 Peroperative heart rate (HR), mean arterial pressure (MAP), and cardiac index (CI) (median (interquartiles)). a=before incision, b=before clamping, c=5 min after clamping, d=after completion of the vascular anastomoses, e=end of operation. There were no inter-group differences

	Measurement time				
	a	b	c	d	e
HR (beat min^{-1})					
Felodipine	79 (68–87)	89 (73–99)	84 (75–94)	80 (73–95)	83 (71–89)
Placebo	81 (68–93)	79 (72–92)	79 (65–84)	76 (60–92)	80 (64–84)
MAP (mm Hg)					
Felodipine	68 (65–73)	83 (79–90)	89 (81–97)	70 (65–72)	76 (68–79)
Placebo	74 (67–85)	82 (74–91)	88 (86–93)	72 (67–80)	79 (69–97)
CI (litre min^{-1} m^{-2})					
Felodipine	3.7 (3.4–3.9)	3.7 (3.4–4.2)	3.7 (3.1–4.2)	3.4 (3.2–4.2)	4.0 (3.2–4.6)
Placebo	3.6 (3.1–4.3)	3.8 (3.3–4.8)	3.3 (2.9–3.9)	3.8 (3.1–4.3)	3.9 (3.5–4.5)

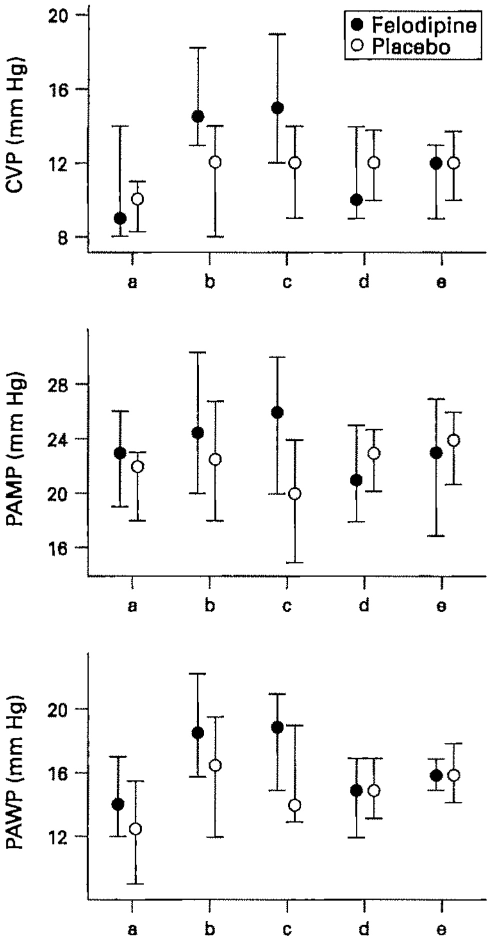

Figure 1 Peroperative haemodynamics in the felodipine and placebo groups (median and interquartiles). Central venous pressure (CVP), pulmonary artery mean pressure (PAMP) or pulmonary artery wedge pressure (PAW) did not differ between groups. There was a time–treatment interaction for CVP and PAMP. a=Before incision, b= before aortic clamping, c=5 min after clamping, d=after completion of the vascular anastomoses, and e=end of operation.

are expected during major vascular procedures.

RENAL HAEMODYNAMICS

The two groups did not differ in ERPF and there was no time–treatment interaction. In both groups ERPF was increased at the first postoperative clearance test (felodipine $P=0.004$; placebo $P=0.002$) compared with the preoperative level (fig. 2). GFR (fig. 2) did not differ in the two groups, there was a

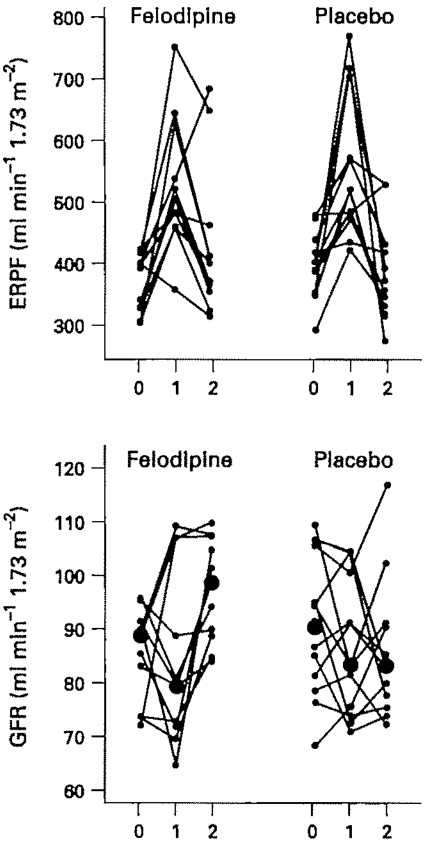

Figure 2 Effective renal plasma flow (ERPF) and glomerular filtration rate (GFR) (means of 2–3 measurements) in the felodipine and placebo groups at: 0=preoperative measurement, 1=first postoperative measurement (haemodynamic stability 1 h after operation), 2=second postoperative measurement (24 h after operation). ERPF: there was no difference between groups, but ERPF was increased at the first postoperative clearance test in both groups compared with preoperative levels. GFR: there was no difference between groups but there was a time–treatment interaction, and GFR was increased 24 h after operation in the felodipine group compared with preoperative values. ●=Median value.

Table 4 Fractional excretion of sodium (FE_{Na}), fractional excretion of potassium (FE_K), osmolar clearance (C_{osm}), and free water clearance (C_{H_2O}) (median (interquartiles)). 0=Preoperative measurement; 1=first postoperative measurement (haemodynamically stable, 1 h after operation); 2=second postoperative measurement (24 h after operation). FE_{Na}, FE_K, C_{osm}, and C_{H_2O}: no inter-group differences, C_{H_2O}: time–treatment interaction. Intra-group differences: $^{**}P<0.01$. Data at first and second postoperative clearances were compared with preoperative clearance

	Measurement time		
	0	1	2
FE_{Na}			
Felodipine	0.012 (0.012–0.020)	0.018 (0.010–0.035)	0.002 (0.001–0.003)**
Placebo	0.014 (0.008–0.017)	0.028 (0.013–0.048)	0.001 (0.001–0.003)**
FE_K			
Felodipine	0.26 (0.22–0.31)	0.35 (0.26–0.43)	0.16 (0.12–0.19)**
Placebo	0.29 (0.20–0.33)	0.39 (0.29–0.44)	0.15 (0.13–0.18)**
C_{osm} (ml min^{-1})			
Felodipine	2.86 (2.33–3.09)	3.31 (1.58–3.73)	1.47 (1.28–1.54)**
Placebo	2.42 (1.98–2.91)	3.45 (2.34–5.18)	1.15 (1.00–1.46)**
C_{H_2O} (ml min^{-1})			
Felodipine	3.72 (2.38–4.84)	−1.01 (−1.42 to −0.36)**	−0.77 (−0.96 to −0.67)**
Placebo	4.62 (4 32–5.75)	−1.07 (−1.46 to −0.79)**	−0.66 (−0.76 to −0.54)**

Table 5 Aldosterone and arginine vasopressin (AVP) concentrations (median (interquartiles)). 0=Preoperative measurement; 1=first postoperative measurement (haemodynamically stable, 1 h after operation); 2=second postoperative measurement (24 h after operation). No inter-group difference for aldosterone and arginine vasopressin. Intra-group differences: $^{**}P<0.01$. Data at first and second postoperative measurements were compared with preoperative measurement

	Measurement time		
	0	1	2
Aldosterone (pmol litre^{-1})			
Felodipine	42 (42–61)	111 (58–197)**	56 (42–117)
Placebo	44 (42–81)	132 (65–144)**	64 (42–96)
AVP (pmol litre^{-1})			
Felodipine	0.5 (0.4–0.7)	83 (41–150) **	3.0 (2.2–12)**
Placebo	0.5 (0.3–0.6)	82 (26–111)**	5.8 (2.7–30)**

time–treatment interaction (P=0.049) and GFR was increased 24 h after operation in the felodipine group compared with preoperative values (P=0.016). The two groups did not differ in filtration fraction, and there was no time–treatment interaction. In both groups the filtration fraction was lower at the first postoperative clearance test than at the preoperative test.

WATER AND ELECTROLYTE CLEARANCE

Urine output was similar in the two groups: 310 (160–560) ml in the felodipine group compared with 490 (236–950) ml in the placebo group during operation, and 1815 (1494–2270) ml in the felodipine group and 2023 (1438–2385) ml in the placebo group until the next morning.

Fractional sodium excretion, fractional potassium excretion and osmolar clearance did not differ between the two groups, and there was no time–treatment interaction. Intra-group differences are shown in table 4. Free water clearance did not differ between groups, but there was a time–treatment interaction (P=0.027). Intra-group differences are shown in table 4.

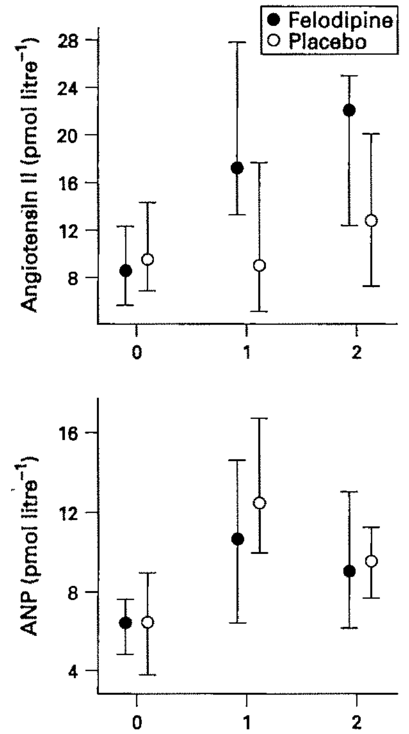

Figure 3 Angiotensin II and atrial natriuretic peptide concentrations (median and interquartiles) in the felodipine and placebo groups. 0= Preoperative measurement, 1=first postoperative measurement (haemodynamically stable, 1 h after operation), 2=second postoperative measurement (24 h after operation). Angiotensin II: there were no inter-group differences but angiotensin II concentrations were increased in the felodipine group at both postoperative clearance tests. ANP: there were no inter-group difference but ANP concentrations were increased at both postoperative clearance tests in both groups.

VASOACTIVE HORMONES

There were no group differences or time–treatment interactions for angiotensin II, aldosterone, atrial natriuretic peptide or vasopressin concentrations. In the felodipine group, angiotensin II was increased at both postoperative clearance tests compared with preoperative values, and ANP was increased in both groups for both tests after operation compared with preoperative values (fig. 3). Aldosterone concentrations were increased to three times preoperative levels at the first postoperative clearance test but returned to preoperative values after 24 h (table 5). Vasopressin concentrations were increased at the first postoperative clearance test and within a very broad range.

PLASMA CONCENTRATIONS OF FELODIPINE

Plasma concentrations of felodipine were 1.04 (0.82–1.63) nmol litre^{-1}, 1 h after operation and 0.30 (0.24–0.43) nmol litre^{-1}, 24 h after operation. The increase in GFR 24 h after operation compared with preoperative values did not correlate with felodipine concentrations.

Discussion

Felodipine did not improve postoperative renal function compared with placebo, and ERPF and GFR were not reduced in the placebo group. The increased GFR, 24 h after operation in the felodipine group, may indicate a beneficial effect of felodipine but in the present context it was not clinically important. Using the same clearance method, Gamulin and colleagues[1 2] demonstrated intraoperative reduction in renal blood flow and GFR after infrarenal aortic clamping. We undertook a postoperative study as it was not possible to maintain stable central and renal haemodynamics during surgery; these are necessary to achieve valid results.

The plasma concentrations of felodipine were less than the therapeutic level for antihypertensive treatment, the lower level being 2.5 nmol litre^{-1}.[10] To our knowledge the therapeutic plasma concentration for prevention of renal ischaemic damage is unknown.

Ours is the first randomized, placebo-controlled study of the renal effects of administration of a calcium antagonist in abdominal aortic surgery. Our results did not establish any benefit from treatment with low-dose felodipine, but the number of patients was small and there was a risk of a type II error. Our results did not excluded the possibility that felodipine may be beneficial in patients with a higher risk of reduced renal function after operation or that felodipine may be beneficial at higher plasma concentrations. The use of dopamine and high filling pressures may have prevented postoperative deterioration in renal function and therefore masked any effect of felodipine.

There was a difference between the groups in administration of vasoconstrictors. The increased ERPF at the first postoperative clearance test in both groups can be attributed to dopamine[11] as the effect of vasoconstrictors administered during operation had disappeared at this stage. ERPF measured 24 h after operation was similar to preoperative values, even during treatment with felodipine. ERPF values in the placebo group indicated neither renal vascular vasoconstriction nor vasodilatation at this stage.

Urine output and fractional excretion of sodium did not differ between the groups. Felodipine has natriuretic and diuretic effects immediately after single dose administration but these effects are less pronounced after days of drug administration.[12, 13]

Patients had an excellent outcome. Complications were minor in the context of postoperative morbidity after major vascular surgery.[14, 15] Patients in our study were a selected group without symptomatic coronary atherosclerosis. The complication rate was the same as in the treatment group in our previous study,[11] which compared the effect of dopamine 3 μg kg^{-1} min^{-1} with placebo in a similar population with the same anaesthetic and operative procedures. The conclusion of that study was that low-dose dopamine relieved cardiovascular depression caused by combined extensive thoracic extradural block and general anaesthesia, and therefore an inotropic adjuvant should accompany this anaesthetic technique.

Felodipine was tolerated well, and side effects were the same in the placebo group. In hypertensive patients, the expected cardiovascular effect of felodipine is a reduction in arterial pressure because of lower peripheral vascular resistance and a higher cardiac index.[16] During operation, mean arterial pressure, heart rate, cardiac index and systemic vascular resistance index were the same in the two groups. Any possible effect of felodipine was not discernible in the presence of operative stress, anaesthesia and low-dose dopamine. The reason for the slightly higher central venous arterial pressure and mean pulmonary artery pressure in the felodipine group is not obvious. Cardiac index did not differ between the groups which indicates that there was no severe depression of ventricular function. Pulmonary artery wedge pressure showed the same trend but was not significant. One would expect concentrations of atrial natriuretic peptide to differ between groups if the trend in these pressures represented imminent heart failure.

Administration of a dihydropyridine calcium antagonist was accompanied by increased plasma concentrations of angiotensin II and unchanged plasma aldosterone concentrations.[12, 17] In this study, aldosterone was increased after operation as expected, but there was no difference between the groups. Twenty-four hours after operation aldosterone concentrations were the same as those measured before operation which may indicate that fluid administration was adequate. Perhaps ANP was increased after operation in both groups as an indication of generous fluid treatment but the levels were moderate compared with those found in heart failure.[18, 19] Our observations mirror the modulating balance between the vasoconstrictor/sodium-retaining effect of the renin–angiotensin–aldosterone system and the vasodilating/diuretic–natriuretic effects of the natriuretic peptides.[20] AVP increased after operation, as observed previously in patients treated with low-dose dopamine,[11] whereas AVP was not increased after operation in the placebo group.[11] Nausea and opioids are well known triggers of AVP release,[21, 22] but the physiological significance of this finding is not obvious.

Acknowledgements

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Effects of temperature on phrenic nerve and diaphragmatic function during cardiac surgery

G. H. MILLS, Z. P. KHAN, J. MOXHAM, J. DESAI, A. FORSYTH AND J. PONTE

Summary

We have studied the effects of whole body cooling on phrenic nerve and diaphragmatic function in 26 patients using magnetic stimulation of the phrenic nerves with a pair of Magstim 200 HP stimulator coils during cardiopulmonary bypass. The diaphragmatic electromyogram in response to magnetic pulses was recorded with needle electrodes at two temperatures, approximately 31 °C (cold) and approximately 36 °C (warm) during the cooling or rewarming phase of hypothermic cardiopulmonary bypass. This 5-°C temperature change was associated with clear changes in the evoked electromyographical response of the diaphragm. Median latency between stimulus and electromyographic response was 10.1 (range 8.0–11.8) ms during cold and 8.3 (5.9–10.2) ms during warm stimulation ($P<0.001$). Median duration of the muscle compound action potential was prolonged and its amplitude reduced in cold compared with warm stimulations ($P<0.01$). These effects were enhanced by application of ice slush to the heart. We conclude that diaphragmatic function may be affected by mild hypothermia after cardiac surgery. (*Br. J. Anaesth.* 1997; **79**: 726–732).

Key words
Temperature, effect. Heart, cardiopulmonary bypass. Surgery, cardiovascular. Muscle skeletal, diaphragm.

Diaphragmatic dysfunction and phrenic nerve injury are well recognized complications of cardiac surgery that often require prolonged ventilatory support.[1] One possible cause of diaphragmatic dysfunction is exposure of the phrenic nerves to ice slush during cardiopulmonary bypass. Moderate cooling of the phrenic nerves or the diaphragm in animals[2–4] has been shown to slow the velocity of nerve conduction and to prolong the muscle action potential, effects also observed in other skeletal muscle groups.[5–8] Exposure of the phrenic nerve to ice slush has also been studied in animals and shown to cause phrenic nerve conduction block proportional to exposure time,[3 4 9] but similar human studies are lacking. The technique of magnetic stimulation of the diaphragm[10 11] is well suited to study the effects of local cooling on phrenic nerve and diaphragm function during cardiopulmonary bypass, causing minimal interference with the course of surgery.

In the absence of gross cardiac or diaphragmatic dysfunction, many centres are aiming to reduce the time of postoperative ventilation in cardiac surgery, usually extubating the trachea of patients within 4 h of surgery. It is believed generally, however, that when patients are hypothermic (<36 °C) on arrival in recovery, mechanical ventilation should be maintained until a core temperature of 37 °C is reached, thus imposing a considerable limitation to the "fast tracking" of these patients. There is, however, no direct evidence that the function of the human diaphragm is impaired by mild hypothermia.

In this study our aim was to document the effects of moderate whole body hypothermia (31–32 °C) and the use of ice slush around the heart on diaphragmatic function.

Patients and methods

The study was approved by the King's Healthcare Ethics Committee and informed consent was obtained from 26 consecutive patients (seven females) referred for coronary artery surgery. Patients with neurological conditions or diabetes were excluded. Morphometric data and cardiopulmonary bypass times are shown in table 1.

ANAESTHETIC MANAGEMENT

Patients were premedicated with temazepam 30 mg, ranitidine 150 mg, papaveretum 11.5 mg and hyoscine 0.3 mg, and anaesthesia was induced with a bolus dose of propofol 50–100 mg and fentanyl 0.5 mg. Anaesthesia was maintained with an infusion of propofol at a rate of 5–10 mg kg^{-1} h^{-1} throughout, and another bolus of fentanyl 0.5 mg before sternotomy. Intubation of the trachea was facilitated by the use of a single dose of either vecuronium 0.08 mg kg^{-1} (20 patients) or suxamethonium 1 mg kg^{-1} (six patients) and no

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GARY H. MILLS, FRCA, JOHN MOXHAM, MD, MRCP (Department of Thoracic Medicine); ZAHID KHAN, FRCA, JOSÉ PONTE, PHD, FRCA (Department of Anaesthetics); JATIN DESAI, FRCS, ANDREW FORSYTH, FRACS (Department of Cardiothoracic Surgery); King's College Hospital, Denmark Hill, London SE5 9RS. Accepted for publication: August 6, 1997.

Correspondence to J. P.

Table 1 Morphometric data for the 26 patients included in the study (mean (SD) or median (range). CPB=Cardiopulmonary bypass time; X-clamp=aortic cross-clamping time; cold–warm=time elapsed between recording the evoked EMG in the cold test condition and the warm test condition at the end of bypass

Age (yr)	60.0 (39–74)
Weight (kg)	80.7 (12.5)
Body mass index	27.8 (3.8)
CPB (min)	82.4 (23.6)
X-clamp (min)	51.7 (14.2)
Cold–warm (min)	22.6 (10.8)

further doses of neuromuscular blocking agents were given throughout surgery.

SURGICAL MANAGEMENT

All patients had three or four coronary grafts performed. The two mammary arteries were dissected in all patients. During cardiopulmonary bypass, all patients were cooled actively to a nasopharyngeal temperature of 32 °C during suturing of the distal ends of the grafts and then warmed to 38 °C before restoring normal circulation. Preservation of the myocardium was achieved with intermittent perfusion of the coronary system via the root of the aorta with blood containing (mmol litre^{-1}): KCl 16, MgCl 16 and procaine 1, at 10–11 °C. Sixteen of the 26 patients also had one single application of ice slush around the heart, without insulating pads. Durations of cardiopulmonary bypass and clamping of the aortic root were noted for all patients (table 1). No patient was receiving inotropes during or before the periods of testing diaphragmatic responses to phrenic stimulation.

RECORDINGS OF DIAPHRAGMATIC EVOKED EMG SIGNALS

After sternotomy, fine needle electrodes were inserted into the thickness of the anterior quadrant of the left hemidiaphragm, approximately 5 cm from the rib insertions, parallel to the muscle fibres. A fine needle temperature sensor was also inserted into the diaphragm in the vicinity of the electrodes. The left hemidiaphragm was chosen because the highest incidence of phrenic dysfunction has been reported on this side.[12–14] The phrenic nerves were stimulated with a 43-mm mean diameter double magnetic coil placed on the anterolateral surface of the neck over the left phrenic nerve. Two double coils were used when both phrenic nerves were stimulated simultaneously.[10 11] Each double coil was powered by a Magstim 200 HP stimulator (Magstim Company, Whitland, Dyfed, Wales). Five consecutive supramaximal stimulations at 15-s intervals, at 100% of maximum stimulator power, were performed at each temperature and the results averaged. The magnetic technique was selected because of the ease with which the phrenic nerve can be stimulated reproducibly. Compared with electrical stimulation, magnetic stimulation is more effective in achieving supramaximal stimulation of the phrenic nerve and is far less sensitive to positioning of the electrodes.[10] The output of the magnetic stimulator was set to maximum in this study, ensuring reliable supramaximal stimulation of the phrenic nerves, as documented in a previous study using the same device.[10] The diaphragmatic evoked electromyograms (EMG) were recorded via sterilized needle electrodes linked to a Magstim Neurosign 2000 amplifier designed for use with patients. The analogue EMG signal was converted to digital form on a National Instruments 12 bit NB-MIO 16 board (National Instruments, Austin, TX, USA) and stored in a MacIntosh 650 Quadra computer (Apple Computer Company, Cupertino, CA, USA). The EMG signal was sampled at 10 kHz and processed on-line using a program developed on LabView 2.2 software (National Instruments, Austin, TX, USA). The magnetic pulse stimulation of the phrenic nerves consistently evoked a compound action potential in the EMG tracing recorded from the diaphragm by the needle electrodes (fig. 1).

The electromyographical measurements were made in all 26 patients: (a) during cardiopulmonary bypass, before re-warming, while the diaphragmatic temperature was approximately 31 °C; and (b) after whole body rewarming when the diaphragmatic temperature was approximately 36 °C. In four of the 16 patients who received ice slush on the heart, an additional set of 13 measurements was obtained (c), the first just before applying the ice slush, the subsequent 11 measurements at 5-min intervals for 55 min and the last measurement at the latest possible time before closing the chest. In six patients whose nasopharyngeal temperatures remained at or above 36 °C at the time of opening the chest and did not receive ice slush, additional electromyographical measurements were made (d) shortly after sternotomy and (e) during the active cooling period at the beginning of cardiopulmonary bypass.

Most of the temperature related data were obtained at the transition from cold to warm occurring at the end of cardiopulmonary bypass, rather than at the transition from warm to cold at the beginning of bypass, for two reasons: first, to allow more time for possible residual effects of the neuromuscular blocking agent (used only to facilitate intubation of the trachea) to dissipate and for stable plasma concentrations of propofol to be achieved; second, most patients had a nasopharyngeal temperature of less than 36 °C at induction of anaesthesia and by the time the chest was opened, most had cooled passively to 34–35 °C. In six subjects whose nasopharyngeal temperature had not decreased to less than 36 °C when the chest was opened, recordings (d) and (e) were also made. These additional data allowed us to observe if the changes occurring during cooling were similar to those observed during re-warming.

OTHER MEASUREMENTS

Temperature measurements were made in the nasopharynx with a standard thermocouple sensor and in the diaphragm with a fine myocardial needle thermocouple sensor (Ellab A/S, Roedovre, Denmark) placed close to the EMG electrodes. At the time of stimulation, diaphragmatic temperature might differ from nasopharyngeal temperature by 0.5–1 °C. It was diaphragmatic temperature, however, that was noted for the purpose of the study although nasopharyngeal temperature was used as a guide for perfusion.

Arterial blood pH, $P\text{CO}_2$ and $P\text{O}_2$, and plasma concentrations of sodium, potassium and calcium were measured at the time of phrenic nerve stimulation using a self-calibrating Ciba-Corning 288 Blood Gas System, available in the same room. Plasma concentrations of propofol were measured when the electrophysiological tests (a) and (b) were performed.

Gastric pressures (Pgas cm H_2O) were measured after simultaneous stimulation of both phrenic nerves in four patients. A 100-cm balloon catheter (PK Morgan, Rainham, Kent, UK) was passed through the nose into the stomach at the start of operation with the aid of a lubricated size 7 uncuffed and uncut red rubber nasotracheal tube. Recordings were obtained with regularly tested[15] Validyne MP45 pressure transducers and amplifiers (Validyne Corporation, Northridge, CA, USA). The mean values of peak amplitudes of four deflections were calculated at two temperatures. Oesophageal pressure recordings were not made during surgery because the chest was open.

Video recordings of the diaphragm during the five phrenic stimulations at each temperature were made in two patients. These were edited subsequently to visually compare the cold and warm twitch responses in quick succession.

ANALYSIS OF DATA

An example of an evoked compound action potential of the diaphragm obtained with the needle electrodes is shown in figure 1. Three values were derived from the evoked EMG trace, as indicated in figure 1: (a) "latency" or time elapsed between the magnetic stimulus artefact and the first deflection of the EMG trace (ms); (b) "duration" or time elapsed between the first deflection and the second peak of the compound action potential (ms); and (c) "amplitude" or magnitude (mV) of the difference between the positive and negative peak deflections of the compound action potential. Absolute amplitude values (mV) were very variable from patient to patient because of the relative positioning of the recording needle electrodes. Therefore, for the tables and for comparison purposes, we decided to express all amplitude values as relative changes with respect to the first set of measurements obtained during the cold period which were taken as 100. In the six patients in whom the warm to cold transition was also studied, the warm value was set to 100 for that set of measurements only. Latency, duration and amplitude were compared between cold (approximately 31 °C, diaphragmatic temperature) and warm (approximately 36 °C) conditions using the Wilcoxon signed rank test. A non-parametric test was used to process these data because of the obvious skew in the distribution. These comparisons were obtained independently for the two subsets of patients who received and who did not receive ice slush. Based on previous studies, the upper limit of normal for latency was taken as 9.5 ms.[16]

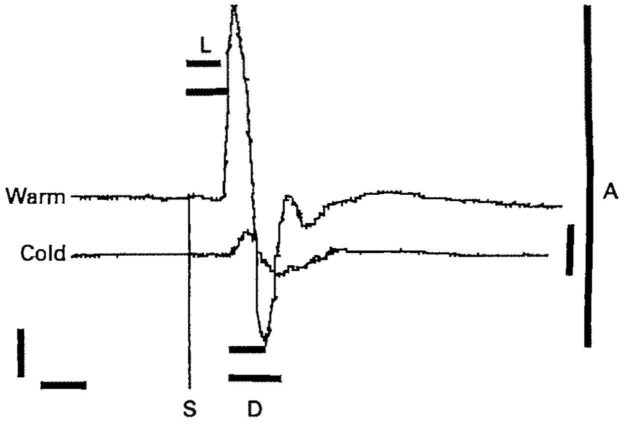

Figure 1 Representative example of two evoked compound action potentials recorded directly from the left diaphragm using needle electrodes, in response to pulses of magnetic stimulation to the left phrenic nerve in one patient. Recordings were made at two diaphragmatic temperatures: first, cold (approximately 31 °C) and 12 min later, warm (approximately 36 °C). S=Stimulus artefact; L=latency (the bars represent the latencies between stimulus and the first deflection in "cold" and "warm" conditions); D=durations between the first deflection and the peak on the second wave; and A=amplitudes of the "warm" and "cold" conditions. On the bottom lefthand corner, horizontal bar=10 ms and vertical bar=0.2 mV.

The influence of possible changes in other factors which might have occurred simultaneously with the change in temperature was also tested. Plasma concentrations of propofol, sodium (Na^+), potassium (K^+) and calcium (Ca^{++}), and arterial blood-gas tensions were compared between cold and warm periods for each of these factors using the paired t test. Duration of cardiopulmonary bypass and aortic cross-clamping time were recorded.

Results

TEMPERATURE OF THE DIAPHRAGM

Before starting warming at the end of cardiopulmonary bypass, mean diaphragmatic temperature was 31.3 (SD 1.87) °C when the cold set of measurements were obtained; nasopharyngeal temperature was at the target value of 32 °C. As the warm end-point of 38 °C in the nasopharynx was reached, mean diaphragmatic temperature was only 36.5 (1.44) °C when the second, warm set of measurements were obtained. This 1.5-°C difference between diaphragmatic and nasopharyngeal temperatures was only reduced slightly (<0.5 °C) in the course of the ensuing 5–10 min after the set of warm measurements were obtained and before cardiopulmonary bypass was discontinued. Thus a gradient of approximately 1 °C between diaphragmatic and nasopharyngeal temperatures was nearly always present at the end of bypass.

PLASMA VARIABLES, CARDIOPULMONARY BYPASS VARIABLES AND BODY TEMPERATURE CHANGES

Plasma concentrations of propofol (total range 0.54–5.33 μg ml^{-1}), Na^+ and Ca^{++}, and arterial blood-gas values did not differ (paired *t* test, except for pH where the Wilcoxon sign rank test was used) between the cold and warm test conditions. Only plasma K^+ concentration was significantly different in the two conditions ($P=0.03$), being higher during the warm condition by 0.28 mmol litre^{-1}.

CHANGES IN LATENCY, DURATION AND AMPLITUDE OF THE EVOKED DIAPHRAGMATIC EMG ASSOCIATED WITH CHANGES IN TEMPERATURE

An example of the effect of a change in temperature from 31 to 36 °C on the evoked muscle action potential in one patient is shown in figure 1. Data relating diaphragmatic evoked EMG latency, duration and amplitude to diaphragmatic temperature are summarized in table 2 for all patients and for two subgroups, those who did and those who did not receive ice slush. Comparisons between cold and warm conditions for all patients showed significant differences for the three variables; percentage changes in latency, duration and amplitude were −18, −14 and +99%, respectively.

Direct observation of the twitch contractions of the diaphragm in response to the magnetic pulses showed an obvious difference between the cold and warm testing conditions in all patients. The contraction was more vigorous and shorter in duration under warm conditions. This difference was clear in the edited video recordings in two patients.

Table 2 Changes in the diaphragmatic evoked EMG in response to magnetic pulse phrenic stimulation in 26 patients, at two temperatures: cold (31.3 °C) and warm (36.5 °C). L=Latency, D=duration and A=amplitude of the evoked compound action potential as a percentage change from the cold condition. Values are medians (range). The Wilcoxon signed rank test was used for comparisons. Data from the 26 patients were first analysed as one population and also as two separate subgroups (those who received ice slush for myocardial preservation and those who did not)

	Cold	Warm	*P*
All (*n*=26)			
L (ms)	10.1 (8.0–11.8)	8.3 (5.9–10.2)	<0.001
D (ms)	11.8 (2.4–26.3)	9.0 (3.3–24.8)	<0.001
A	100	123 (53–1410)	<0.05
Ice (*n*=16)			
L (ms)	10.3 (8.0–11.8)	7.9 (6.1–10.2)	<0.001
D (ms)	10.6 (2.4–26.3)	8.6 (3.3–22.9)	<0.001
A	100	123 (74–313)	<0.05
No ice (*n*=10)			
L (ms)	9.8 (8.2–11.2)	8.7 (5.9–9.8)	<0.01
D (ms)	12.8 (5.5–23.1)	9.8 (5.7–24.8)	ns
A	100	153 (53–1410)	ns

Table 3 Changes in the diaphragmatic evoked EMG in response to magnetic pulse phrenic stimulation in six patients during a temperature transition from warm (36 °C) to cold (32 °C). Units of measurement and symbols are as in table 2, except that the baseline value for A was in the warm condition

n=6	Warm	Cold	*P*
L (ms)	8.6 (7.5–9.2)	10.9 (9.0–11.8)	<0.05
D (ms)	8.2 (5.8–11.7)	9.4 (5.5–13.8)	ns
A	100	13.9 (10–34)	ns

In the subgroup of six patients also tested during the transition from warm to cold, the mean diaphragmatic "warm" temperature was 34.8 °C (36 °C in the nasopharynx) and "cold" 31.5 °C. On cooling, latency increased significantly by 25% and there were no significant changes in duration (12% increase) or amplitude (80% decrease, see table 3).

A comparison between the subgroup of six patients who received suxamethonium and the subgroup of 20 patients who received vecuronium for intubation of the trachea showed no differences in the EMG variables latency, duration and amplitude between the cold and warm set of measurements.

IMMEDIATE EFFECTS OF ICE SLUSH ON PHRENIC NERVE CONDUCTION

The use of ice slush reduced markedly the amplitude of the left evoked diaphragmatic EMG within 5 min in the four patients monitored throughout the ice slush application, and increased markedly latency and duration, as seen in figure 2. In two of the patients the EMG was abolished during the initial 10 min of ice slush use, no diaphragmatic movement being visible in response to phrenic stimulation. Thus data on latency and duration could not be recorded during this period. Within 15 min, the EMG started to recover and after 55 min the mean values for latency, duration and amplitude were, respectively, 134%, 127% and 76% of pre-ice

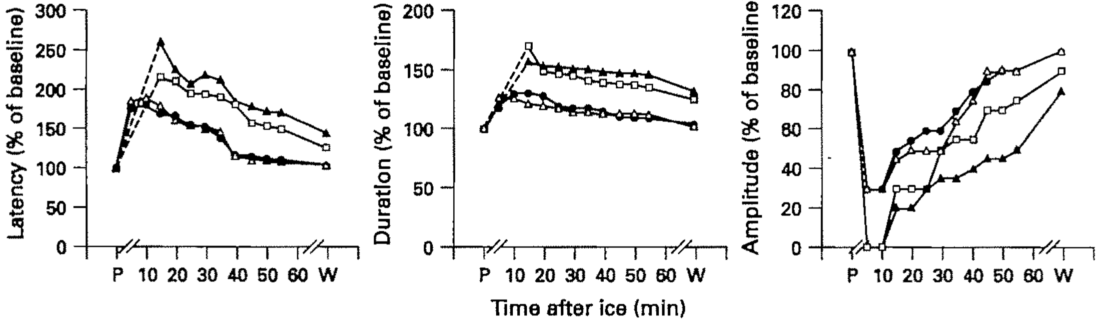

Figure 2 Changes in latency, duration and amplitude, as percentages from baseline pre-ice slush values (P), in the diaphragmatic EMG compound action potential evoked by magnetic pulse stimulation of the left phrenic nerve, in four patients. Values were recorded at 5-min intervals after application of ice slush to the heart and also after systemic warming, just before chest closure (W). In two patients (□ and ▲) the evoked EMG was abolished for 10 min after ice application.

values. By the time the chest was closed, mean values for latency, duration and amplitude were 118%, 115% and 92% of pre-ice values. Only three of the 26 patients failed to recover the latency of the evoked EMG response to within the normal range (less than 9.5 ms) by the end of surgery; two of these patients had received ice slush, but none had difficulty in weaning from mechanical ventilation after surgery. All patients were breathing spontaneously within 6 h of arrival in the recovery ward.

CHANGES IN GASTRIC PRESSURE IN RESPONSE TO PHRENIC STIMULATION

The amplitude of the gastric pressure deflections in response to bilateral phrenic stimulation was more variable from patient to patient than the EMG data. Within each patient, however, variability was comparable with that of the EMG data. The amplitude of the deflection was approximately double during warm compared with cold stimulation in the four patients studied.

Discussion

The main finding in this study was the shortening of latency and increase in amplitude of the evoked diaphragmatic EMG action potential associated with a 5-°C increase in temperature. Even the smaller temperature change (3.3 °C) in the six patients studied during the warm to cold transition caused a significant increase in latency. These findings are not surprising, but provide the first direct evidence of the effects of small changes in temperature on phrenic nerve and diaphragmatic function in humans. This observation is important because the temperatures tested (31, 34.8 and 36 °C) were within the range likely to be found during recovery from major surgery.

Another observation was the marked reduction in amplitude of the EMG of the left hemidiaphragm shortly after a single application of ice slush to the heart. It appeared to temporarily abolish the diaphragmatic twitch response to phrenic stimulation within 10–15 min in approximately 50% of patients (two of four in our series), without subsequent long-term dysfunction.

LIMITATIONS OF THIS STUDY

An important limitation of this study was the emphasis placed on the electromyographic variables to describe the function of the diaphragm. Ideally, we should have measured changes in twitch tension of the diaphragm in response to impulse stimuli, a notoriously difficult technique, only possible in animal experiments. In human studies, measurement of changes in transdiaphragmatic pressure in response to bilateral twitch stimulation of the diaphragm would have been the technique of choice to assess function, provided the chest cavity was not open. As the opportunity of obtaining measurements during relatively rapid changes in temperature occurred only with the chest open, we had no choice in the method of assessing diaphragmatic function other than the EMG and direct observation of diaphragmatic movement. The video recordings of the twitch responses were useful to confirm the impression gained from direct observation but did not provide quantitative data. Intragastric pressure measurements carried out in four patients during bilateral phrenic stimulation aimed at demonstrating a mechanical correlate of the EMG changes. These results, however, must be interpreted with caution because of many factors (for example, the presence of an open chest distorted by the chest retractor) which may have affected the absolute magnitude of the responses. Nevertheless, despite patient-to-patient variation in the amplitude of the baseline pressure deflection, it doubled with the increase in temperature in all four patients tested, which strongly supports the EMG data.

The results obtained, however, simply suggest that there was a degree of muscle weakness associated with 3–5 °C of hypothermia. They do not allow us to predict if this weakness induces a corresponding degree of hypoventilation in a spontaneously ventilating hypothermic patient. A different type of study design, with emphasis on breathing variables, is required to answer this question. It is generally recognized, however, the difficulty in correlating EMG findings with postoperative diaphragm dysfunction.

Ideally, each set of measurements should start with baseline EMG responses at normothermia followed by measurements during hypothermia and then recovery to normothermia. This approach was not possible in the majority of our patients because nasopharyngeal temperature was less than 36 °C after induction of anaesthesia or had decreased to 34–35 °C by the time the chest was open.

The observed effects on the EMG are unlikely to be related to the anaesthetic drugs used. Plasma propofol concentrations were within the range of light anaesthesia and decreased slightly, but not significantly, between measurements. I.v. induction agents have been shown to reduce the amplitude of the leg EMG response to magnetic cortical stimulation[17 18] whereas fentanyl has no effects. Data are not available on the direct effects of anaesthetic agents on the motor neurone, skeletal muscle or the neuromuscular junction, except for volatile agents which depress the EMG response evoked by cortical stimulation[19] and the excitability of spinal motor neurones.[20] Vecuronium, used for intubation of the trachea in 20 patients, could have affected the EMG responses as there is evidence that hypothermia prolongs its effect.[21] It is unlikely that vecuronium could account for the changes in EMG variables observed during the short period of systemic warming (approximately 15 min) occurring at least 3 h after the single bolus administration of a moderate dose for intubation. The identical responses observed in the six patients given suxamethonium for intubation also refutes a possible effect of residual block. We do not have a plausible explanation for the slight but significant increase in mean plasma potassium concentration associated with systemic warming. It was, however, too small to have physiological effects and did not correlate with individual changes in electrophysiological variables.

CHANGES IN DIAPHRAGMATIC EMG WITH HYPOTHERMIA

On the transition from cold to warm in the 10 patients not exposed to ice slush, the only significant change was the shortening of latency in the evoked EMG response. The lack of significance in the changes in duration and amplitude may be explained by the greater variability in the measurements of duration and amplitude, especially amplitude which was sensitive to small changes in electrode position. In the smaller subgroup of six patients in whom measurements were also made during the transition from warm to cold, again, only latency showed a significant change with cooling, despite the smaller sample size and the smaller temperature change (mean 3.3 °C). The variability in the measurements in this subgroup was noticeably reduced, perhaps because the patient's systemic cooling took place over a much shorter period of time than warming, so the interval between the measurements at the two temperatures was shorter.

EFFECTS OF ICE SLUSH

The duration of the conduction block which we observed with ice slush was much shorter than that reported previously in a similar experimental situation in dogs. Exposure of the dog phrenic nerve to ice slush for 30–60 min caused total phrenic block with a similar, rapid onset (approximately 5 min) but lasting between 6 and 28 days[9] instead of 10–15 min as in our study. This discrepancy may be because of the pericardial sac preventing direct contact between the slush and the phrenic nerve. Duration of exposure to ice may also be important. Rosou and colleagues,[13] who studied patients in whom a special cooling jacket was placed around the heart for much longer periods of time, observed a 23% incidence of prolonged phrenic paresis. It may be noteworthy that two of the three subjects in our study who, despite normothermia had a prolonged latency at the time of chest closure (but no subsequent clinically obvious postoperative dysfunction) had been exposed to ice slush. We did not, however, expect to be able to correlate measurements obtained during surgery with measurements of diaphragmatic dysfunction observed after surgery in such a small number of patients. Given the average incidence of severe diaphragmatic dysfunction after cardiac surgery, it would require study of at least 400 consecutive patients to be able to include one with this complication. The fact that all patients in this study had an uneventful recovery and were breathing spontaneously 6 h after surgery does not exclude the presence of diaphragmatic dysfunction, especially during the first 3 h of recovery. A different study design is required to examine the effects of postoperative hypothermia on respiratory variables.

The clinical implications of our study are mostly apparent when attempts are made to reduce the time to extubation after cardiac anaesthesia (often referred to as "fast tracking"). Most patients, if normothermic, are able to maintain acceptable gas exchange when spontaneous ventilation returns shortly after closure of the skin. If hypothermia is present, however, there is diaphragmatic dysfunction and we believe that some type of mechanical assistance to breathing is justified until normothermia is achieved, especially in susceptible patients such as the elderly or the obese.

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Changes in regulators of the circulation in patients undergoing lung surgery

J. Boldt, M. Papsdorf, D. Uphus, M. Müller and G. Hempelmann

Summary

Several vasoactive substances are responsible for control of the circulation. During lung surgery these substances may be influenced either by the technique of anaesthesia or by altered production and elimination. We have studied plasma concentrations of important regulators of the circulation in patients undergoing lobectomy using two different regimens: propofol–low-dose fentanyl–nitrous oxide–vecuronium, tracheal extubation immediately after surgery (group Ia (n=15)); fentanyl–midazolam–pancuronium, delayed tracheal extubation in the intensive care unit (ICU) (group Ib (n=15)). We also studied patients undergoing pneumonectomy using fentanyl–midazolam–pancuronium anaesthesia (group II (n=15)). Plasma concentrations of endothelin-1 (ET-1), atrial natriuretic peptide (ANP), vasopressin, catecholamines (adrenaline, noradrenaline) and 6-keto-prostaglandin F_{1alpha} were measured. Extensive haemodynamic monitoring was performed using a pulmonary artery catheter. All measurements were carried out after induction of anaesthesia (baseline values), 30 min after one-lung ventilation (OLV) was induced, at the end of surgery, 2 h after surgery in the ICU and on the first day after operation. CVP, PAP and PCWP increased in all groups during OLV but remained increased only in patients undergoing pneumonectomy. CI decreased significantly in the pneumonectomy group but did not differ between both lobectomy groups. SVRI was lowest in the propofol-treated patients and remained highest in the pneumonectomy group. Plasma concentrations of adrenaline and noradrenaline did not change in group Ia, but increased significantly in groups Ib (noradrenaline: from 267 (67) to 496 (91) pg ml^{-1}) and II (adrenaline: from 237 (59) to 681 (210) pg ml^{-1}). Plasma concentrations of ET-1 remained almost unchanged in groups Ia and Ib, whereas they increased in pneumonectomy patients (from 2.63 (0.3) to 6.61 (1.01) pg ml^{-1}). Vasopressin plasma concentrations increased during OLV in all groups; they were lowest in the propofol patients and highest in patients undergoing pneumonectomy (32.2 (10.2) pg ml^{-1}). Plasma concentrations of ANP and 6-keto-prostaglandin F_{1alpha} increased in all groups during OLV and remained increased only in the pneumonectomy group. (*Br. J. Anaesth.* 1997; **79**: 733–739).

Key words
Surgery, thoracic. Cardiovascular system, responses. Sympathetic nervous system, catecholamines. Sympathetic nervous system. Ventilation, one lung.

During major surgery, circulatory stability is of major importance for patient outcome.[1] Functional disturbances in the microcirculation must also be avoided because it has become increasingly clear that reduction in microcirculatory blood flow is an important trigger for the development of multiple organ dysfunction syndrome.[2] Neural control mechanisms and various circulating vasoactive substances are involved in the control of organ perfusion in this situation. Humoral agents which are known to alter (micro-) circulatory blood flow include adrenaline, noradrenaline and vasopressin. Atrial natriuretic peptide (ANP) has been detected more recently and it participates in the regulation of vasomotor tone either directly by affecting vascular tone or indirectly by influencing hormone homeostasis (e.g. renin release, modifying catecholamine synthesis).[3 4]

In recent years there has been a large body of literature suggesting that the vascular endothelium is involved in the regulation of regional microcirculatory blood flow.[5] Among the substances released from the endothelium to maintain haemostasis and circulatory homeostasis is the 21-amino acid endothelin-1.[6 7] It appears to have a greater vasoconstrictor effect than any other substance, including vasopressin and noradrenaline. Its vasoconstrictive potency is approximately 10 times that of angiotensin II.[6] In addition to the vascular properties of endothelin-1, interactions with other vasoactive substances may be important (e.g. inhibition of release of catecholamines and renin, stimulation of ANP release).[8] The interactions between these (often opposing) vasoactive forces ultimately determine systemic and regional blood flow.[9]

During thoracic surgery this regulatory system

J. Boldt*, MD, Department of Anaesthesiology and Intensive Care Medicine, Klinikum der Stadt Ludwigshafen, Ludwigshafen, Germany. M Papsdorf, D. Uphus, M Müller, MD, G. Hempelmann, MD, Department of Anaesthesiology and Intensive Care Medicine, Justus-Liebig-University Giessen, Giessen, Germany. Accepted for publication: July 30, 1997

*Address for correspondence: Department of Anaesthesiology and Intensive Care Medicine, Klinikum der Stadt Ludwigshafen, Bremserstr. 79, D-67063 Ludwigshafen, Germany.

may be altered by many mechanisms. Surgical stress, the lateral position in association with one-lung ventilation (OLV), clamping of the pulmonary artery and the anaesthetic regimen may result in changes in plasma concentrations of vasoactive substances. It is known that the lung serves not only gas exchange but is also involved in the regulation of circulatory homeostasis: some vasoactive substances are produced by the lung (e.g. angiotensin II, prostaglandins) and others are taken up from the circulation and metabolized (e.g. endothelin, catecholamines).[10–12] Thus surgery of the lung may have a profound influence on regulators of the macro- and microperfusion. This study was designed to determine the influence of different anaesthetic management regimens and different types of lung surgery on plasma concentrations of important vasoactive substances.

Patients and methods

After obtaining institutional review and written informed consent, we studied 30 patients undergoing lobectomy (group I) and 15 patients undergoing pneumonectomy (group II), both caused by primary lung cancer. Mediastinal lymph nodes were dissected extensively in all patients. Patients with renal insufficiency (creatinine >1.5 mg dl^{-1}), liver dysfunction (aspartate aminotransferase (AST) >40 iu $litre^{-1}$, alanine aminotransferase (ALT) >40 iu $litre^{-1}$) or preoperative pulmonary hypertension (mean pulmonary artery arterial pressure (PAP) >30 mm Hg) were excluded. No patient had a history of myocardial infarction in the previous 6 months or had documented valvular heart disease.

Patients in group I were separated into one of two groups before operation according to a randomized sequence. In group Ia ($n=15$), propofol was given for induction of anaesthesia followed by a continuous infusion until the end of operation (range 0.05–0.15 mg kg^{-1} min^{-1}). Fentanyl 2.5 μg kg^{-1} was given for induction of anaesthesia followed by administration of additional fentanyl if necessary (maximum dose 0.5 mg). Propofol infusion was supplemented with 66% nitrous oxide in oxygen. Neuromuscular block was produced by vecuronium. In these patients the trachea was extubated immediately after surgery and the patient taken to the intensive care unit (ICU), breathing spontaneously. In group Ib (standard management, $n=15$), induction of anaesthesia was carried out with thiopentone 400–500 mg, fentanyl 0.1 mg and pancuronium 0.1 mg kg^{-1}. For additional anaesthesia, fentanyl, midazolam and pancuronium were given according to the patient's clinical response. An oxygen–air mixture was used. Mechanical ventilation was continued in the ICU in these patients for at least 2 h after surgery. The trachea was extubated when haemodynamic and respiratory variables remained stable for at least 30 min. Group II ($n=15$) included patients undergoing pneumonectomy and fentanyl–midazolam–pancuronium were used for anaesthesia (same technique as in group Ib). Controlled mechanical ventilation was continued in the ICU until patients breathed spontaneously and cardiorespiratory variables remained stable.

A double-lumen endobronchial tube was used to carry out one-lung ventilation (OLV). Controlled mechanical ventilation was adjusted to maintain Pa_{O_2} at 15–20 kPa and Pa_{CO_2} at 5.3–5.7 kPa. When necessary, 100% oxygen was used during the period of one-lung ventilation (OLV) (aim Sp_{O_2} >90%). In groups 1b and II the double-lumen tube was replaced by a standard tube at the end of surgery.

Extensive intercostal nerve block was performed directly by the surgeon before closure of the chest (0.5% bupivacaine 1.5 mg kg^{-1}). In the ICU, additional intercostal nerve block was used when the patient felt pain and/or piritramide was given i.v. After tracheal extubation, all patients received oxygen 3 litre min^{-1} by nasal tube.

Fluid (low molecular weight hydroxyethylstarch solution (LMW-HES) or Ringer's solution, or both, was given to maintain central venous pressure (CVP) at 10–14 mm Hg throughout the study, packed red blood cells (PRBC) were administered when haemoglobin was <9 g dl^{-1}. Respiratory complications were defined as the need for mechanical ventilation for more than 24 h and cardiocirculatory complications were defined as the need for inotropic support (adrenaline, noradrenaline). The therapeutic management of all patients (volume replacement, pharmacological support, ventilation patterns) was performed by physicians who were not involved in the study.

MEASURED VARIABLES AND DATA POINTS

Heart rate (HR), mean arterial pressure (MAP), pulmonary artery pressure (PAP), pulmonary capillary wedge pressure (PCWP), central venous pressure (CVP) and cardiac output (CO, thermodilution technique) were monitored using a pulmonary artery catheter. From arterial blood samples, plasma concentrations of endothelin-1 (ET-1) were measured by radioimmunoassay (RIA) (Biocode, Sclessin, Belgium[13]). Blood samples were collected in tubes containing 5 mg of editic acid (ethylenedinitro tetraacetic acid) and plasma was separated immediately by centrifugation and stored at −35 °C until analysis. As provided by the manufacturer, normal plasma values in healthy volunteers are 2–4 pg ml^{-1}, the sensitivity of the RIA was 0.5 pg ml^{-1}, and cross reactivity with ET-1 was 100%, with ET-2 34%, with ET-3 64%, with big-ET 2% and with other vasoactive peptides (e.g. angiotensin I and II, bradykinin, ANP) <0.1%. Atrial natriuretic peptide (ANP) (by RIA; Instar Corp., Stillwater, MN, USA[14]), vasopressin (by RIA; Instar Corp., Stillwater, MN, USA[15]), 6-keto-prostaglandin F_{1alpha} (the stable but inactive end product of prostaglandin I_2 (prostacyclin)), using a commercially available enzyme immunoassay kit (TiterZyme, PerSeptive Diagnostics, Cambridge, MA, USA) and catecholamines (adrenaline and noradrenaline; by a high-pressure liquid chromatographic (HPLC) technique with electrochemical detection) were also analysed from arterial blood samples. Standard laboratory variables were also monitored.

Measurements were performed after induction of anaesthesia (supine position, after haemodynamic stability was reached=baseline values), 30 min after atelectasis was induced (=one-lung ventilation (OLV), lateral position), at the end of surgery (supine position), 2 h after the end of surgery (in the ICU) and at the morning of the first day after operation (supine position, in the ICU).

STATISTICAL ANALYSIS

All variables are expressed as mean (SD). One- and two-factorial analyses of variance for repeated measurements (ANOVA, including Scheffe`s test) were used for statistical analysis. Additionally, the Mann–Whitney *U* test and chi-square test were used when appropriate. $P<0.05$ was considered significant.

Results

Patients undergoing pneumonectomy were at higher risk (higher ASA classification) than those undergoing lobectomy (table 1). Three patients undergoing pneumonectomy died during the intensive care period. In patients in group Ia the trachea was extubated at 31 (10) min, in group Ib, 345 (111) min and in patients undergoing pneumonectomy at 611 (219) min after surgery (table 1). Cumulative fluid balance was higher in propofol-treated patients than in the other two groups.

HAEMODYNAMIC STATE

MAP increased significantly during and after OLV in groups Ib and II (table 2). CVP, PAP and PCWP remained increased after OLV only in patients undergoing pneumonectomy, while they normalized in groups Ia and Ib (table 2). CI decreased significantly in patients undergoing pneumonectomy but did not differ in the two other groups. SVRI was lowest in the propofol-treated group and remained highest in patients undergoing pneumonectomy. Pa_{O_2}/FI_{O_2} ratio was comparable in both lobectomy groups (table 2). Pneumonectomy patients showed a significantly lower Pa_{O_2}/FI_{O_2} ratio than those in the groups undergoing lobectomy.

REGULATORS OF THE CIRCULATION

Plasma concentrations of noradrenaline (fig. 1) did not change in propofol-treated patients (group Ia) but increased significantly in the two other groups (group Ib, from 267 (67) to 496 (91) pg ml^{-1} at the end of surgery; group II, from 237 (59) to 681 (210) pg m^{-1}). Plasma concentrations of adrenaline (fig. 1) also increased only in patients in groups Ib and II. ET-1 plasma concentrations remained almost unchanged in groups Ia and Ib (fig. 2). It increased significantly in patients in group II (from 2.63 (0.3) to 6.61 (1.01) pg ml^{-1} at the end of the study). In the perioperative period, vasopressin plasma concentrations (fig. 2) increased similarly in all groups. Two hours after surgery vasopressin concentrations were significantly lower in group Ia (increase from 2.23 (0.88) to 14.8 (3.1) pg ml^{-1}) and significantly higher in patients undergoing pneumonectomy (increase from 2.58 (0.79) to 32.2 (10.2) pg ml^{-1}). On the morning of the first day after operation, plasma concentrations of vasopressin were still significantly highest in the pneumonectomy group (16.9 (3.9) pg ml^{-1}). Plasma concentrations of ANP and 6-keto-prostaglandin F_{1alpha} increased significantly in all groups during OLV (fig. 3). ANP concentrations

Table 1 Patient and perioperative data (mean (SD or range) or number) in group Ia (lobectomy patients using propofol), group IIb (lobectomy using fentanyl/midazolam) and group II (pneumonectomy patients). OLV=One-lung ventilation; po=postoperative; L=left side; R=right side; FEV_1=forced expiratory volume in 1 s (% of vital capacity); VC=vital capacity; HES=hydroxyethylstarch solution; PRBC=packed red blood cells. *$P<0.05$ compared with other groups

	Group Ia (n=15)	Group Ib (n=15)	Group II (n=15)
Age (yr)	66.5 (55–72)	65.5 (52–75)	64.1 (54–71)
Weight (kg)	77.1 (12.2)	78.2 (10.2)	81.1 (10 7)
ASA	I:3; II:6; III:4; IV:2	I:2; II:7; III:4; IV:2	I:1; II:4; III:6; IV:4*
Surgery (n)			
Left/right pneumonectomy	—	—	L=7/R=8
Lobectomy	L:9/R:6	L:8/R:7	—
Non-survivors	—	—	3
Preoperative lung function			
FEV_1 (%)	67 (9)	70 (10)	65 (8)
VC (litre)	3.83 (0.7)	3.61 (0.9)	3.09 (0.6)
Time of surgery (min)	167 (56	173 (71	172 (66)
OLV (min)	49 (21)	51 (20)	—
Extubated after surgery (min)	31 (10)	345 (111)	611 (219)*
Total amount of drugs at the end of surgery			
Fentanyl (mg)	0.39 (0.04)*	2.1 (0.3)	2.3 (0.4)
Midazolam (mg)	—	20.1 (2.1)	22.9 (3.9)
Vecuronium (mg)	4.1 (2.2	—	—
Pancuronium	—	8.4 (2.7)	10.9 (2.5)
Cumulative volume therapy (until 1st postoperative day)			
Ringer`s solution (ml)	2.350 (500)	2.650 (550)	2.650 (550)
HES (ml)	850 (250)*	350 (250)	400 (250)
Total units PRBC per group	3	4	8

Table 2 Changes in mean arterial pressure (MAP), heart rate (HR), pulmonary artery pressure (PAP), pulmonary capillary wedge pressure (PCWP), central venous pressure (CVP), cardiac index (CI), systemic vascular resistance index (SVRI) and Pa_{O_2}/FI_{O_2} ratio (mean (SD)) in group Ia (lobectomy patients using propofol) IIb (lobectomy using fentanyl–midazolam) and group II (pneumonectomy patients). OLV=one-lung ventilation; po=postoperative. *$P<0.05$ compared with other groups; †$P<0.05$compared with baseline values

Variable	Group	After induction	30 min OLV	End of surgery	2 h after surgery	1st po day
MAP	Ia	76.2 (9.5)	80.1 (8.9)	78.9 (10.1)	80.1 (11.5)	89.1 (9.8)†
(mm Hg)	Ib	78.9 (7.9)	91.2 (10.4)*†	90.2 (11.2)*†	90.9 (10.1)*†	91.0 (11.1)†
	II	79.5 (10.1)	92.3 (11.7)*†	94.1 (12.2)*†	92.1 (11.4)*†	93.0 (11.4)†
HR	Ia	77 (11)	70 (11)	71 (12)	80 (12)	82 (13)
(min^{-1})	Ib	78 (12)	92 (10)*†	90 (9)*†	91 (11)*†	85 (12)
	II	79 (12)	94 (13)*†	92 (11)*†	94 (13)*†	85 (12)
PAP	Ia	19.9 (3.2)	24.4 (4.3)†	20.4 (3.4)	20.1 (3.3)	20.2 (3.1)
(mm Hg)	Ib	20.1 (2.5)	28.9 (3.8)*†	22.2 (3.5	21.6 (3.0)	21.1 (3.0)
	II	20.5 (3.0)	29.1 (3.4)*†	27.7 (3.5)*†	27.5 (3.2)*†	25.4 (3.5)*†
CVP	Ia	11.2 (2.2)	13.2 (2.2)†	10.9 (2.9)	9.9 (2.1)	9.2 (2.1)
(mm Hg)	Ib	10.5 (3.1)	14.1 (2.6)†	10.8 (2.3)	10.1 (2.8)	10.1 (2.3)
	II	10.1 (2.7)	14.5 (3.0)†	13 9 (3.2)*†	13.2 (3.2)*†	13.9 (3.7)*†
PCWP	Ia	11.1 (3.1)	14.7 (3.6)†	12.5 (3.3)	11.5 (2.2)	10.9 (2.1)
(mm Hg)	Ib	11.8 (2.1)	15.2 (4.0)†	12.1 (4.1)	11.6 (2.6)	10.8 (3.2)
	II	12.0 (2.0)	17.0 (4.4)†	18.4 (3.2)*†	15.3 (3.3)*†	13.9 (2.3)*†
CI	Ia	2.74 (0.5	2.86 (0.6)	3.31 (0.6)	3.20 (0.5)	3.50 (0.6)
(litre min^{-1} m^{-2})	Ib	2.81 (0.4)	2.51 (0.5)	3.10 (0.5)	3.28 (0.6)	3.42 (0.5)
	II	2.72 (0.5)	2.43 (0.4)	2.50 (0.5)*	2.81 (0.4)*	2.80 (0.5)*
SVRI	Ia	1895 (233)	2009 (311)	1537 (288)	1739 (356)	1820 (287)
(dyn s cm^{-5} m^{-2})	Ib	1930 (256)	2491 (317)*†	2176 (303)*	2020 (310)*	1978 (319)
	II	1978 (239)	2449 (307)*†	2541 (317)*†	2390 (293)*†	2392 (297)*†
Pa_{O_2}/FI_{O_2}	Ia	384 (61)	292 (88)†	410 (87)	401 (67)	413 (69)
(mm Hg)	Ib	377 (75)	268 (79)†	389 (92)	395 (58)	391 (76)
	II	341 (68)	232 (77)†	321 (95)*	327 (65)*	303 (70)*

returned to baseline values in groups Ia and Ib thereafter, but were still significantly higher in the pneumonectomy group at the end of the study (115.5 (13.1) pg ml^{-1}). Plasma concentrations of 6-keto-prostaglandin F_{1alpha} remained significantly increased until the end of the study in patients undergoing pneumonectomy (60.4 (8.8) pg ml^{-1}).

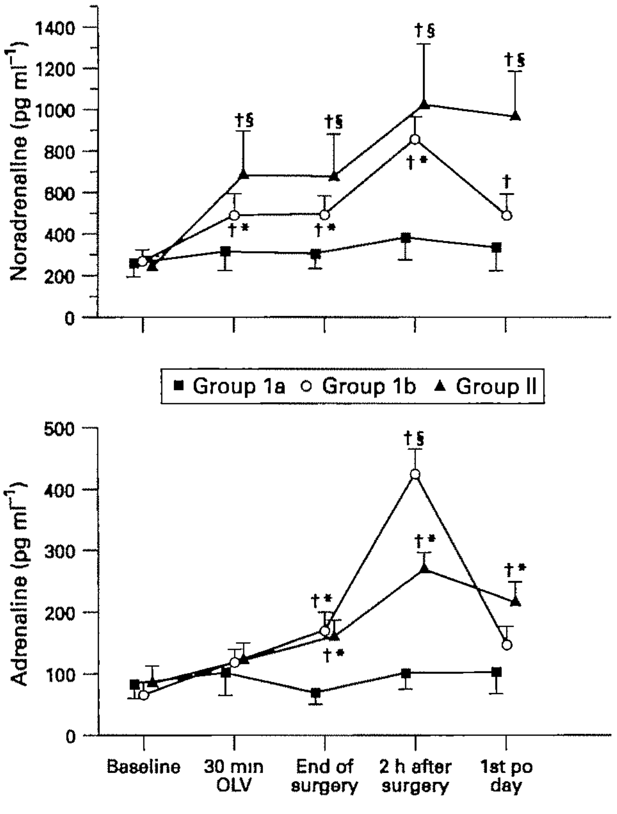

Figure 1 Changes in plasma concentrations of noradrenaline (normal range 180–250 pg ml^{-1}) and adrenaline (normal range 30–85 pg ml^{-1}) in group Ia (propofol patients who underwent tracheal extubation immediately after surgery), group Ib (midazolam–fentanyl patients, extubation in the ICU) and group II (pneumonectomy patients). $P<0.05$ compared with: *group Ia; †baseline values; §groups Ia and Ib.

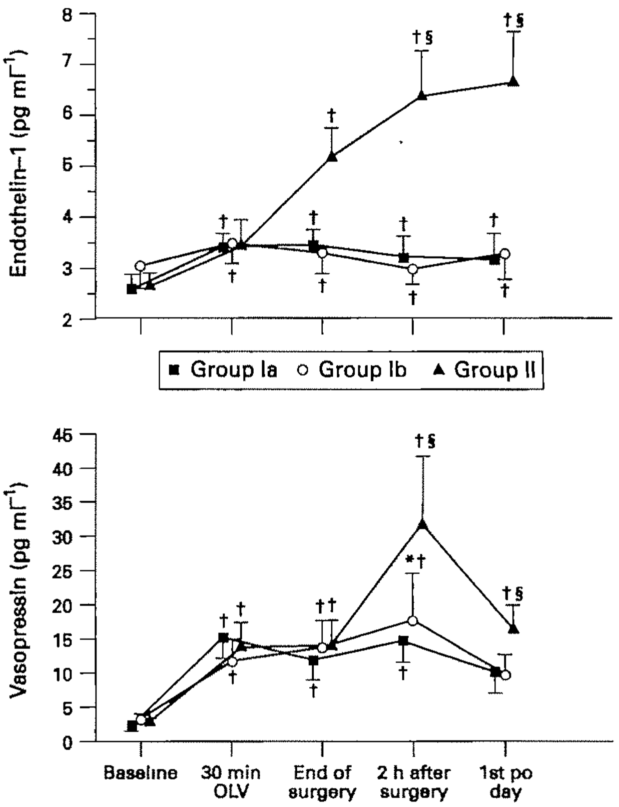

Figure 2 Changes in plasma concentrations of vasopressin (normal range <3.0 pg ml^{-1}) and endothelin-1 (normal range 2.0–5.0 pg ml^{-1}) in the three groups (see fig. 1 for details). $P<0.05$ compared with: *group Ia; †baseline values; §groups Ia and Ib

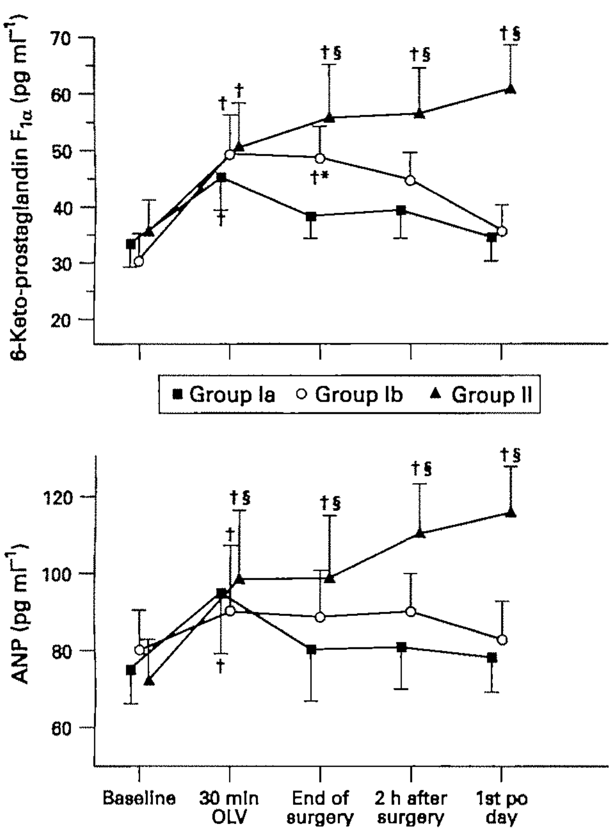

Figure 3 Changes in plasma concentrations of 6-keto-prostaglandin F_{1alpha} (normal values <30 pg ml^{-1}) and atrial natriuretic peptide (ANP) (normal values 20–80 pg ml^{-1}) in the three groups (see fig. 1 for details). $P<0.05$ compared with: *group Ia; †baseline values; §groups Ia and Ib.

Discussion

We found that propofol-treated patients showed early co-operation, were orientated, could sigh and cough on command, and effective physiotherapy was possible earlier in the postoperative period than in the other lobectomy group. Haemodynamic variables in the propofol group were almost comparable with patients in whom an anaesthetic regimen with longer acting anaesthetic substances (midazolam–fentanyl–pancuronium (standard management technique) and subsequent delayed extubation in the ICU were used. CI was slightly higher in propofol-treated patients, possibly because of a lower SVR than in the other group. PAP during OLV was also lower in the propofol than in the other group indicating less increase in right ventricular work. MAP remained stable in propofol-treated patients, probably because of adequate volume replacement which is known to prevent unwanted hypotension during propofol infusion. Plasma concentrations of catecholamines were significantly higher in the anaesthetic regimen with delayed extubation than in propofol-treated patients who underwent extubation immediately after surgery. All other vasoactive substances (ET-1, vasopressin, ANP, 6-keto-prostaglandin F_{1alpha}) were similar between the two groups during the study.

PNEUMONECTOMY PATIENTS

Patients undergoing pneumonectomy showed significant differences both in haemodynamic state and vasoactive regulators of the circulation compared with patients in group Ib in whom the same anaesthetic technique was used. PAP increased during OLV and remained higher than baseline until the end of the study. In a study by Lewis and co-workers,[16] including 20 patients with moderately severe chronic obstructive pulmonary disease undergoing pneumonectomy, only 10% had a normal PAP in the immediate postoperative period. Others also reported a marked increase in right ventricular afterload during OLV and after completion of resection.[16–18] Increased right ventricular (RV) afterload in this situation most likely results from increased pulmonary vascular constriction secondary to hypoxic vasoconstriction (HPV), pulmonary microvascular plugging and decreased pulmonary vascular compliance.[17]

Plasma concentrations of potent vasoconstrictive substances (e.g. vasopressin, ET-1, noradrenaline) increased significantly in patients undergoing pneumonectomy. All are potent vasopressors which may act particularly in the intestinal circulation with detrimental consequences for the organism.[19] Activation of the sympathetic system is caused by a complex interaction of different stimuli, for example hypotension, hypovolaemia and hypoperfusion. The increase in plasma concentrations of catecholamines reflects the magnitude of the (reflectory) sympathetic nervous system response in this situation. In recent years it has become obvious that in addition to "systemic" regulators of the circulation (e.g. catecholamines), substances released by the endothelium are also involved in the pathophysiology of circulatory abnormalities.[20 21] ET-1 is one of these substances which can induce regional vasoconstriction followed by impaired organ blood flow. ET-1 is released by pathophysiological states that are characterized by limitation of cardiac output or by hypotension. Apart from the direct vasoconstrictive actions of ET-1, it may also influence the circulation by altering other regulator systems. Thus ET-1 was reported to stimulate the release of catecholamines and renin[22] thus possibly contributing to vasoconstriction and reduced blood flow at the microcirculatory level. In contrast, ET-1 also influences ANP secretion increasing circulating ANP in dogs[23 24]: ANP may function as a negative feedback regulator of ET-1 and the vasoconstrictive actions of ET-1 are opposed by the release of other vasoactive substances, including ANP.

Plasma concentrations of ANP were significantly increased in the pneumonectomy group. A linear relationship between ANP plasma concentrations and right atrial (RAP) and pulmonary capillary wedge pressure (PCWP) has been shown.[25] However, this may not be the only mechanism by which plasma concentrations of ANP were increased. Endothelin has been shown to stimulate release of ANP *in vivo* and *in vitro*.[26] Both substances have important interactions on the vascular level: ANP appears to counteract the contractile response to endothelin.[27] Additionally, results from animal and human studies suggest that adrenaline (which was also increased in pneumonectomy patients) stimulates ANP secretion.[24] 6-Keto-prostaglandin F_{1alpha} was also increased in the pneumonectomy patients. Nakae and colleagues[28] showed that it may serve as a marker of illness severity. Pneumonectomy patients showed delayed stabilization of haemodynamic state and pulmonary function resulting in delayed tracheal extubation in the ICU. Thus it can be assumed that these were at higher risk of developing cardiopulmonary complications.

The significant changes in plasma concentrations of potent vasoactive substances may have important consequences for organ function. Altered microregional vascular tone results in some capillary regions being over perfused while others are under perfused.[29] Although three of the 15 pneumonectomy patients and none of the lobectomy patients died during their stay in the intensive care unit, the population was too small to draw definite conclusions on whether or not the measured vasoactive substances were responsible for the difference in survival rates between the groups.

The reasons for the more pronounced changes in important regulators of the circulation in the pneumonectomy patients can only be speculative. It is unlikely that the technique of anaesthesia was the major reason because lobectomy patients in group Ib underwent the same anaesthetic management (midazolam–fentanyl–pancuronium) but showed only moderate changes in plasma concentrations of the vasoactive substances. As indicated by the higher ASA classification, severity of illness in the pneumonectomy patients appeared to be higher than in the two lobectomy groups resulting in less cardiopulmonary reserve. Last but not least, altered production or uptake may be the reason for the increased plasma concentrations of some of the vasoactive substances. There is convincing evidence that the lung is a highly metabolic organ which contributes markedly to production and elimination of various substances (e.g. noradrenaline, prostaglandins, ANP). Endothelial cells appear to play a particular role in this process. The pulmonary endothelium has an immense surface area and actively participates in production and inactivation of vasoactive substances.[30] As an example, the lung is apparently the most relevant organ in rapid clearance of endothelin.[31] The pulmonary circulation also has the potential to generate endothelin from its own endothelium given an appropriate stimulus such as hypoxia.[23] This may be one explanation for the higher plasma concentrations of ET-1 in our pneumonectomy patients. The lung may also participate in regulation of the action of ANP secreted by the right atrium by active metabolism.[4] Interactions of ET-1 with other vasoactive substances may have further influenced their plasma concentrations (e.g. inhibition of release of catecholamines and renin by ET-1, stimulation of ANP release by ET-1).[8]

In summary, regulation of the macro- and microcirculation is dependent on both centrally originated and locally derived control mechanisms. The anaesthetic regimen in patients undergoing major thoracic surgery was only of limited value in affecting important regulators of the circulation. Thus an anaesthetic regimen using more short acting substances with early tracheal extubation of the patient appeared to be without detrimental effects on the (micro-) circulation. More extensive lung surgery (e.g. pneumonectomy) was followed by more extensive changes in plasma concentrations of important regulators of organ perfusion. As the (micro-) circulatory flow abnormalities appear to be a major determinant of development of organ function further studies are needed to assess whether its manipulation may improve patient outcome.

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I. v. fentanyl decreases the clearance of midazolam

I. HASE, Y. ODA, K. TANAKA, K. MIZUTANI, T. NAKAMOTO AND A. ASADA

Summary

We have examined the effect of fentanyl on the pharmacokinetics of midazolam in patients undergoing orthopaedic surgery. Thirty patients were allocated randomly to receive fentanyl 200 μg and midazolam 0.2 mg kg^{-1} (fentanyl group, n=15) or placebo and midazolam 0.2 mg kg^{-1} (placebo group, n=15) in a double-blind manner for induction of anaesthesia. Anaesthesia was maintained with nitrous oxide and isoflurane. Systemic clearance of midazolam was decreased by 30% (P=0.002) and elimination half-time was prolonged by 50% (P=0.04) in the fentanyl group compared with the placebo group. There were no differences in the distribution half-time or volume of distribution at steady state between the two groups. These findings indicate that elimination of midazolam was inhibited by fentanyl during general anaesthesia. (*Br. J. Anaesth.* 1997; **79**: 740–743).

Key words

Hypnotics benzodiazepine, midazolam. Analgesics opioid, fentanyl. Enzymes, cytochrome P450. Pharmacokinetics, midazolam. Pharmacokinetics, fentanyl.

Midazolam is a widely used anaesthetic with a short duration of action.[1 2] It is metabolized by the hepatic microsomal cytochrome P4503A (CYP3A),[3 4] which is inhibited by various drugs, including antibiotics, antimycotics and calcium channel blocking agents, resulting in prolonged drowsiness and inhibition of psychomotor performance.[5–7] Midazolam is used frequently in combination with opioids for anaesthesia and sedation. CYP3A plays a role in the metabolism of fentanyl[8] and it may occur that one drug inhibits the metabolism of another drug when they are metabolized by the same P450 isozymes.[9] Therefore, the metabolism of midazolam may also be inhibited by simultaneously administered fentanyl, with prolongation of the duration of action of midazolam. Although the pharmacokinetics of midazolam have been studied extensively,[1 2 5–7] the effect of fentanyl on the pharmacokinetics of midazolam has not been elucidated. As midazolam frequently induces hypoxaemia and apnoea when used with fentanyl,[10] it is important to examine the effect of fentanyl on the pharmacokinetics of midazolam. Our objective was to investigate the effect of i.v. fentanyl on the pharmacokinetics of i.v. midazolam.

Patients and methods

The reference substance of midazolam was a gift from Hoffmann-La Roche Ltd (Nutley, USA). Diazepam and fentanyl were purchased from Takeda Pharmaceuticals Co. Ltd (Tokyo, Japan) and from Sankyo Pharmaceuticals Co. Ltd (Tokyo, Japan), respectively. Other reagents and organic solvents were obtained from Wako Pure Chemical Industries (Tokyo, Japan). A C18-column (TSKgel ODS-120T) was obtained from the Tosoh Corp. (Tokyo, Japan).

STUDY DESIGN

We used a double-blind, randomized, placebo-controlled study design with parallel groups. Based on our preliminary study, we determined that 15 patients would be needed in each group to demonstrate a 50% increase in the elimination half-time of midazolam at a level of significance of P=0.05 and power of 80%. Prolongation of the elimination half-time of midazolam inhibits psychomotor performance of patients and delays tracheal extubation after operation.[5 6]

After obtaining approval from the Institutional Ethics Committee and written informed consent, we studied 30 patients, ASA I, aged 17–40 yr, undergoing orthopaedic surgery. Patients were allocated randomly to receive fentanyl or placebo. All staff in the operating room and in the recovery room were unaware of the randomization code. Exclusion criteria were hepatic dysfunction, heart disease, treatment with any known inhibitor or inducer of CYP3A enzymes, and morbid obesity. Patients undergoing laparotomy were also excluded.

All patients were premedicated with secobarbitone 100 mg and atropine 0.5 mg i.m., given 60 min and 30 min before induction of anaesthesia, respectively. Anaesthesia was induced with fentanyl 200 μg i.v.,

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ICHIRO HASE, MD, YUTAKA ODA, MD, KAZUO TANAKA, MD, KOH MIZUTANI, MD, TATSUO NAKAMOTO, MD, AKIRA ASADA, MD, Department of Anaesthesiology and Intensive Care Medicine, Osaka City University Medical School, 1-5-7 Asahimachi, Abeno-ku, Osaka 545, Japan. Accepted for publication: July 22, 1997.

Correspondence to Y. O.

followed by midazolam 0.2 mg kg^{-1} i.v. 1 min later (fentanyl group). Fentanyl was diluted with saline to a total volume of 10 ml and injected over 1 min. In the placebo group, the same volume of saline was administered instead of fentanyl, followed by midazolam 0.2 mg kg^{-1}. Isoflurane and 66% nitrous oxide in oxygen were used to maintain anaesthesia. Tracheal intubation was facilitated with vecuronium 0.1 mg kg^{-1} i.v. After tracheal intubation, the lungs were ventilated to maintain end-tidal carbon dioxide concentration at 4.6–5.3 kPa. End-tidal carbon dioxide tensions and concentrations of isoflurane were measured with a gas analyser (Capnomac Ultima, Datex Instrumentarium Corp., Helsinki, Finland). The minimum alveolar anaesthetic concentration hours (MAC-h) exposure was calculated from the percent anaesthetic concentration and duration of exposure. MAC values of 1.15% were used for isoflurane.[11] The trachea was extubated after operation and patients were transferred to the recovery room.

BLOOD SAMPLING AND MEASUREMENT OF PLASMA CONCENTRATIONS OF MIDAZOLAM

To measure plasma concentrations of midazolam, blood samples were obtained from an indwelling arterial cannula before and 5, 10, 15, 20, 30, 45, 60, 90 and 120 min after administration of midazolam, and every 60 min thereafter until 360 min. Additional blood samples were obtained to measure plasma concentrations of fentanyl at 5, 15, 60 and 180 min after administration of midazolam. Plasma was separated within 30 min and stored at −40°C until analysis. The amount of blood collected for the study was less than 100 ml, and insignificant relative to surgical loss.

Plasma concentrations of midazolam were measured by high-pressure liquid chromatography (HPLC) using a method described previously with modifications.[12] Briefly, HPLC was carried out with a mobile phase consisting of 50% acetonitrile and 0.1% acetate (v/v) in distilled water at a flow rate of 1.5 ml min^{-1} at 45°C, with midazolam and an internal standard, diazepam, detected at a wavelength of 250 nm. The limit of quantitation was 1 ng ml^{-1}. The coefficients of day-to-day variation were 8.6% at 30 ng ml^{-1} (n=18) and 5.1% at 500 ng ml^{-1} (n=17). Fentanyl was quantified by a radioimmunoassay technique as reported previously.[13 14]

PHARMACOKINETIC CALCULATIONS AND STATISTICS

The pharmacokinetics of midazolam were analysed with a two-compartment open model using SAAMII for the Macintosh computer (SAAM Institute, Seattle, WA, USA) as reported previously.[2] The pharmacokinetics of midazolam were characterized by systemic clearance (*Cl*), distribution and elimination half-times ($T_{1/2}{}^{\alpha}$ and $T_{1/2}{}^{\beta}$, respectively) and steady-state volume of distribution (V^{ss}). Systemic clearance was defined as dose/areas under the plasma concentration–time curves (AUC). AUC was calculated by the trapezoidal rule, and other pharmacokinetic variables were calculated using standard formulae.[1] All data are expressed as mean (SD). Patient characteristics and pharmacokinetic variables of the groups were compared using the Student's t test. Data were analysed with the Statview J version 4.5 (Abacus Concepts, Inc., Berkeley, USA) and differences were considered significant if $P<0.05$.

Results

There were no significant differences between the two groups in patient age, weight, height or duration of anaesthesia (table 1). There were no significant differences in isoflurane MAC-h between the two groups. Arterial pressure and heart rates were almost unchanged and there were no differences between the groups at any blood sampling time during the study. All patients awoke immediately after

Table 1 Patient data and details of anaesthesia for the placebo and fentanyl groups (mean (SD or range) or number). Values were compared between groups using the Student's t test. No significant differences between groups

	Placebo group (n=15)	Fentanyl group (n=15)
Sex (M/F)	10/5	9/6
Age (yr)	28 (17–40)	28 (18–40)
Weight (kg)	58 (11)	60 (10)
Height (cm)	167 (6.9)	166 (9.4)
Duration of anaesthesia (min)	268 (92)	219 (123)
Dose of isoflurane (MAC-h)	3.58 (1.25)	3.38 (2.11)

Table 2 Pharmacokinetic variables for midazolam area under the plasma concentration–time curve (AUC), systemic clearance (*Cl*), steady-state volume of distribution (V^{ss}), distribution half-time ($T_{1/2}{}^{\alpha}$) and elimination half-time ($T_{1/2}{}^{\beta}$). Values were compared between groups using the Student's t test

	Placebo group	Fentanyl group	P
AUC(0–∞) (ng ml^{-1} h)	418.5 (96.9)	645.7 (226.8)	0.001
Cl (ml min^{-1} kg^{-1})	8.4 (2.1)	5.9 (1.9)	0.002
V^{ss} (litre kg^{-1})	1.2 (0.5)	1.3 (0.5)	ns
$T_{1/2}{}^{\alpha}$ (min)	17.0 (9.5)	23.3 (8.2)	ns
$T_{1/2}{}^{\beta}$ (min)	146 (62)	217 (114)	0.04

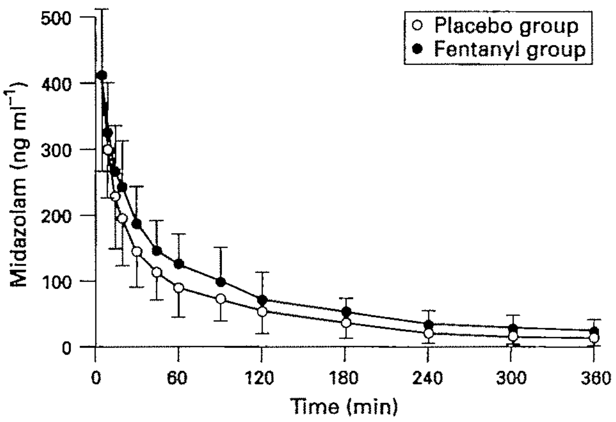

Figure 1 Plasma concentrations of midazolam after i.v. administration of midazolam (mean, SD). Anaesthesia was induced with fentanyl 200 µg and midazolam 0.2 mg kg^{-1} (fentanyl group) or with saline and midazolam 0.2 mg kg^{-1} (placebo group).

discontinuation of inhalation anaesthesia, and the trachea was extubated. No patient developed hypoxia or hypercapnia after operation. Duration of anaesthesia was less than 360 min for 13 patients in the placebo group and for 13 patients in the fentanyl group, and blood sampling was performed in the recovery room after the end of operation.

Systemic clearance, V^{ss}, $T_{1/2}{}^{\alpha}$ and $T_{1/2}{}^{\beta}$ for midazolam in the placebo group were similar to those reported previously.[5 6] There were no differences in V^{ss} or $T_{1/2}{}^{\alpha}$ between the placebo and fentanyl groups (table 2). In the fentanyl group, systemic clearance of midazolam was decreased by 30% ($P=0.002$) and $T_{1/2}{}^{\beta}$ was prolonged by 49% ($P=0.04$) compared with the placebo group, suggesting that elimination of midazolam was prolonged by a single dose of fentanyl administered 1 min before midazolam (fig. 1, table 2). Plasma concentrations of fentanyl were 3.57 (1.29), 1.70 (0.54), 0.78 (0.23) and 0.48 (0.12) ng ml^{-1} at 5, 15, 60 and 180 min after administration of midazolam ($n=6$), and comparable with those reported previously.[15]

Discussion

There are many reports describing the pharmacokinetics of midazolam with or without opioid analgesics,[1 2 5–7] and combined use of midazolam with such analgesics has been shown to have a supra-additive hypnotic effect and to induce respiratory depression.[10 16] However, there have been no studies of the effect of fentanyl on the pharmacokinetics of midazolam. In this study, we found that fentanyl reduced significantly the clearance of midazolam in a anaesthetic procedure commonly used in clinical practice. Plasma concentrations of midazolam were less than the amnesic level at the end of operation, and no patient exhibited delayed emergence from anaesthesia. However, the prolonged effects of midazolam were reported to be a result of inhibition of clearance of midazolam,[6 7] suggesting that persistent amnesia and respiratory depression may occur when midazolam is used with fentanyl.

The pharmacokinetics of midazolam are influenced by agents which are metabolized by CYP3A or influence CYP3A activities, including antibiotics, antimycotics and calcium channel blocking agents.[5–7] As fentanyl is also metabolized selectively by CYP3A,[8] the decrease in systemic clearance of midazolam observed in our study was probably induced by competitive inhibition of CYP3A by fentanyl. Isoflurane is also metabolized by cytochrome P450, whereas CYP2E1 is involved exclusively in the metabolism of isoflurane, and isoflurane has no effect on CYP3A activity.[17 18] We used secobarbitone for premedication in both groups. Although some barbiturates induce CYP3A isoforms, it takes several days to increase the level of CYP3A in the liver and to influence drug metabolism in vivo.[19 20] In this study, plasma concentration of midazolam was measured within 7 h after administration of secobarbitone, suggesting that secobarbitone had no effect on the CYP3A level and pharmacokinetics of midazolam.

Metabolism of midazolam may also be influenced by hepatic blood flow, as the hepatic extraction ratio of midazolam is intermediate.[1] Hepatic blood flow is decreased by hypocapnia, positive pressure ventilation and laparotomy.[21 22] In our study, normocapnia was maintained and no patient underwent laparotomy. Although isoflurane may also affect hepatic blood flow,[23] the mean concentration of isoflurane was comparable in the two groups. Moreover, the pharmacokinetic variables in the placebo group were comparable with those reported for healthy volunteers,[5 6] suggesting that isoflurane and positive pressure ventilation had negligible effects on the pharmacokinetics of midazolam in our study. To our knowledge, there are no reports on the effect of fentanyl on hepatic blood flow in humans *in vivo*. In a study using animals, fentanyl had no effect on hepatic blood flow.[24]

Plasma concentrations of fentanyl in the fentanyl group were comparable with those after i.v. administration to volunteers without concomitant drugs.[15] As wide inter-individual variations are reported for fentanyl pharmacokinetics and pharmacokinetic variables were not obtained as a result of the small number of sampling points in this study,[15] the reason for this finding remains unclear.

Recently, a contribution of CYP3A in the intestine to the metabolism of midazolam has been reported.[25] Because midazolam undergoes first-pass elimination in the intestine, intestinal CYP3A activities should be considered when the pharmacokinetics of orally administered midazolam are analysed.

In summary, we found that the clearance of midazolam was decreased by a single dose of fentanyl, probably as a result of competitive inhibition of CYP3A activity.

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Pharmacodynamics of thiopentone: nocifensive reflex threshold changes correlate with hippocampal electroencephalography

D. P. ARCHER AND S. H. ROTH

Summary

The electroencephalographic (EEG) effects of thiopentone have been used extensively in the pharmacodynamic and pharmacokinetic modelling of drug effects in the central nervous system (CNS). Thiopentone has a biphasic (enhancement followed by inhibition) effect on nocifensive reflexes that occurs in a dose range similar to that which activates the EEG. In this study we have used rats chronically instrumented with hippocampal EEG (hEEG) electrodes to simultaneously characterize the effects of thiopentone on the hEEG and nocifensive reflex thresholds. Enhancement of these two measures of CNS effect correlated well with plasma thiopentone concentrations of 10–30 μg ml^{-1} (35–75 μmol $litre^{-1}$) but maximal reflex enhancement occurred at concentrations of 3 μg ml^{-1} (11 μmol $litre^{-1}$) less than the peak hEEG effect. The results validate the usefulness of nocifensive reflex thresholds for measurement of the CNS effects of thiopentone at subanaesthetic concentrations. (*Br. J. Anaesth.* 1997; **79**: 744–749).

Key words
Anaesthetics i.v., thiopentone. Monitoring, electroencephalography. Anaesthesia, depth. Pharmacodynamics, thiopentone. Rat.

The abolition of the withdrawal response to noxious stimulation (nocifensive response) has been used clinically and experimentally to define the state of surgical anaesthesia.[1] Recent studies (for review see Collins, Kendig and Mason[2]) showed that the anaesthetic effects responsible for suppressing nocifensive responses occurred primarily in the spinal cord. Results from our laboratory[3–5] suggest that nocifensive reflex thresholds provide a measure of anaesthetic depth throughout the entire range of clinically relevant thiopentone concentrations. The effects of thiopentone on nocifensive reflex thresholds are concentration dependent, time independent and constant under pseudo-steady state conditions.[4]

The electroencephalogram (EEG) has been used extensively for pharmacodynamic modelling of the CNS effects of thiopentone.[6] Stanski and colleagues have characterized the pharmacokinetics and pharmacodynamics of the CNS site(s) for the EEG effects of thiopentone.[6 7] As thiopentone distributes rapidly within the brain and the spinal cord,[8] the pharmacokinetic profiles of the drug, as measured by the EEG and nocifensive reflex thresholds, should be directly correlated. The objective of this study was to demonstrate that the pharmacodynamic profiles also correlated well. We measured the hippocampal electroencephalogram (hEEG) which, in the rat, has a pharmacodynamic profile similar to that of the cortical EEG[9 10] and the threshold tail withdrawal from pressure.[3–5] The pharmacodynamic relationships between thiopentone concentrations and both the hEEG and nocifensive reflexes are complex, demonstrating a characteristic biphasic relationship (enhancement followed by depression) between plasma drug concentration and CNS effect.[4 6] In this study we have compared the pharmacodynamics of the hEEG and nociceptive effects of thiopentone.

Materials and methods

The experiments were approved by the Animal Care Committee of the University of Calgary and conformed to the guidelines of the Canadian Council on Animal Care and the International Association for the Study of Pain. Male Sprague–Dawley rats weighing 250–350 g were housed in the vivarium (lights on 06:00–18:00) with food and water *ad libitum* for at least 1 week before testing. All studies were conducted between 10:00 and 15:00.

Two experimental designs were used. The aim of the first (five rats) was to characterize the pharmacodynamic relationships between thiopentone, nocifensive reflex thresholds and the hEEG for the full range of clinically relevant plasma concentrations of thiopentone (0–65 μg ml^{-1}; 0–250 μmol $litre^{-1}$). In the second study (five rats), we examined the correlation between hEEG total power and nocifensive reflex thresholds for hyperalgesic thiopentone concentrations of 0–30 μg ml^{-1} (0–115 μmol $litre^{-1}$).

DAVID P. ARCHER*, MD (Department of Anaesthesia); SHELDON H. ROTH, PHD (Department of Pharmacology and Therapeutics); Faculty of Medicine, University of Calgary, Calgary, Alberta, Canada. Accepted for publication: August 6, 1997.

*Address for correspondence: Department of Anaesthesia, Foothills Hospital, 1403 29th St NW, Calgary, Canada T2N 2T9.

SURGICAL PROCEDURES

Hippocampal electrode insertion

EEG electrodes were inserted into the dentate gyrus of the hippocampal formation as described previously.[11] Briefly, under general anaesthesia (pentobarbitone 50 mg kg^{-1} i.p.), insulated tungsten wires (130 μm in diameter) were inserted bilaterally into the dentate region under stereotactic guidance using the following co-ordinates: 3.4 mm posterior to the bregma, 1.8 mm lateral to the midline and 2.7 mm ventral to the dural surface. The indifferent electrode was an uncoated tungsten wire placed in the cortex. During electrode insertion, spontaneous output from the dentate electrode was monitored on an oscilloscope with an audio monitor. The position of the electrodes was optimized by selecting the region of maximum spontaneous output. Electrodes were fixed with dental acrylic to stainless steel screws threaded into the skull and attached to a connector base mounted to the skull with acrylic. Rats were allowed 1 week to recover from surgery. At that time, inspection of the hEEG confirmed the presence of typical hippocampal theta rhythm in 10 rats that were then studied using the measurement techniques outlined below. Two animals did not demonstrate adequate hEEG 1 week after electrode placement and were excluded from the study. In all animals, movement, feeding and grooming were normal after electrode placement. Histological examination for electrode placement previously demonstrated minimal damage to the hippocampus.[11]

Vascular cannulation

Vascular catheters were inserted into rats that had successful electrode placement. Under general anaesthesia with halothane (2–3% in oxygen), 10 mm of polyethylene tubing (internal diameter 0.58 mm) were inserted into the left femoral artery and vein under direct vision, the wound edges infiltrated with 1% lignocaine and the wound closed. Each animal was partially restrained in a plaster cast, which extended from the ankles to the upper abdomen, and then taped to a wooden block. This technique is used commonly in radioautographic measurements of cerebral blood flow and metabolism, and has been shown not to affect withdrawal reflex thresholds to tail pressure in the rat.[3 12] Animals were allowed 2 h[13] to eliminate halothane. The physiological effects of infusion of thiopentone were assessed with measurements of mean arterial pressure, arterial blood-gas tensions and packed cell volume.

ELECTROENCEPHALOGRAPHIC PROCEDURES

Recordings of hEEG activity were made (180 min) using a Grass model 7D Polygraph with Wide Band AC EEG pre-amplifier model 7P5B (Grass Medical Instruments Co., Quincy, MA, USA). Filter settings were: 1 Hz for the half amplitude low filter and 35 Hz for the half amplitude high filter. Signals were stored on video cassette using a Neuro-corder Interface (Neuro Data Instruments Co., NY, USA, model DR-484) for subsequent spectral analysis. Each hEEG recording was marked audibly for the start of each measure of nociception in the experiment. At each of the planned measurement times in the study, withdrawal latency was measured during a period when the animal was resting quietly. A 27.5-s segment of data recorded just before measurement of withdrawal latency was subjected to power spectral analysis using software developed in this laboratory. Each segment was divided into 2.5-s epochs and the analysed results of 11 epochs were averaged to generate mean values for total power ($voltage^2$/Hz) and power density (proportion of total power) in three frequency bandwidths: 0–4 Hz, 4–12 Hz and 12–25 Hz.

MECHANICAL WITHDRAWAL THRESHOLD

We used analgesimetry to assess the threshold for the nocifensive reflex responses to noxious pressure stimulation in the tail. The threshold for withdrawal of the tail in response to pressure (mechanical withdrawal threshold, MWT) was measured with an Analgesy-Meter (Stoelting Instruments, Chicago, IL, USA), as described previously.[3–5] The end-point of each measurement, the first movement of the tail sufficient to displace the tail from the plinth, was identified by an observer blinded to the instrument scale. A second observer recorded the applied pressure. MWT was calculated as the average of three measurements.

DRUG ADMINISTRATION AND MEASUREMENT

In the first study, each animal was subjected to two timed sequences of MWT testing. During the first (control) sequence, animals received an infusion of saline 0.15 ml min^{-1}; MWT was measured at 0, 2, 4, 6, 8, 12, 16, 20, 25 and 30 min after the start of the infusion. Animals were then allowed a rest period (no stimulation for 60 min) before the second (thiopentone infusion) sequence. An infusion of thiopentone at a rate of 0.67 mg kg^{-1} min^{-1} (2.5 μmol kg^{-1} min^{-1}) in normal saline 0.15 ml min^{-1} was selected on the basis of previous studies.[3–5] The goal was to produce a gradual increase in plasma thiopentone concentration, achieving plasma concentrations of 20–30 μg ml^{-1} (75–115 μmol $litre^{-1}$) by the end of the 30-min infusion and to produce nearly complete suppression of the EEG by 60 min. A plateau in plasma thiopentone concentrations was anticipated to occur after 30 min of infusion, and the infusion rate was doubled at that time. During infusion of thiopentone, MWT was measured in the same time sequence as for the control measurements and then every 10 min, for a total of 70 min.

For the second study, we limited the duration of drug infusion (0.67 mg kg^{-1} min^{-1}; 2.5 μmol kg^{-1} min^{-1}) to 20 min. Measurements of plasma thiopentone concentrations and CNS effect (reflex threshold and hEEG) were made before and at 2, 4, 6, 8, 12, 16 and 20 min after the start of infusion of thiopentone. Arterial blood-gas tensions were measured before and after 20 min of infusion.

Plasma concentrations of thiopentone were measured by HPLC as described previously.[3] The limit of detection was 0.3 μg ml^{-1}, accuracy ±4.5% and coefficient of variation +5%. Shed blood (200 μl per sample) was replaced with three times the volume of normal saline.

DATA ANALYSIS

To facilitate comparison of hEEG and withdrawal response effects of thiopentone on the hEEG, MWT was expressed as a percentage of pretreatment or control values in each rat. We then transformed the withdrawal response data by the function: withdrawal response=1/ MWT×100. This derived variable was then comparable with activation of the hEEG shown by the maximal total power of the EEG which was also expressed as a percentage of pretreatment total power. These data were then analysed for each rat individually for three of the descriptors of a biphasic relationship[6 7]: maximal CNS effect, plasma concentration at maximal effect ($C_p$max) and the plasma concentration at 50% inhibition of the response. The area under the plasma thiopentone–effect curve (AUC), calculated by the linear trapezoidal method, was used to determine the centroid concentration, $C_p$centroid (thiopentone concentration for which the concentration–effect curve is divided equally along the concentration axis). The mean values of the descriptors for hEEG power and withdrawal response were compared by paired Student's *t* test. Statistical significance was taken as $P<0.05$. Results are given as mean (95% confidence interval).

The hEEG pharmacodynamic data obtained in study 1 were analysed by progressive polynomial regression from zero to third order. The "best fit" was selected as the lowest order polynomial that produced a marked increase in the incremental *F* value (*F*=incremental variation from the dependent variable mean/residual variation about the regression curve).

SigmaStat and SigmaPlot software (Jandel Scientific, San Rafael, CA, USA) were used to perform the statistical analyses, graphics and curve fitting.

Results

PHYSIOLOGICAL EFFECTS OF THIOPENTONE

The physiological effects of infusion of thiopentone in study 1 are summarized in table 1. After 30 min of thiopentone infusion, there were no significant deviations in any of these variables from values observed before infusion. As expected, after 60 min of drug infusion, animals were hypotensive, hypothermic and hypoxaemic, with significant respiratory acidosis. Blood letting had also resulted in a decrease in packed cell volume after 60 min. The focus of the study was during the initial 20–30 min of infusion. There were no changes in the physiological variables in any of the animals at any time during the second study (thiopentone infusion limited to 20 min).

STUDY 1: EFFECTS OF THIOPENTONE ON NOCIFENSIVE REFLEX THRESHOLDS

Mean values of MWT were similar when measured before the control infusion (235, 116–354 g), after the control infusion (237, 165–309 g) and before the thiopentone infusion (268, 164–372 g) (repeated measures ANOVA, $P=0.310$). As shown in figure 1, the threshold for withdrawal to tail pressure did not change during the control period, decreased after the start of thiopentone infusion and then increased when plasma concentrations of thiopentone reached 30–40 μg ml^{-1} (110–150 μmol $litre^{-1}$). Plasma concentrations of thiopentone associated with the peak of reflex responsiveness (C_p1/MWT max) were 13 (10–16) μg ml^{-1} (68, 38–98 μmol $litre^{-1}$) (table 2).

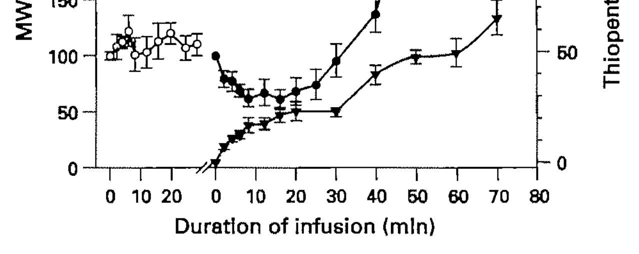

Figure 1 Study 1. Mechanical withdrawal threshold (MWT), expressed as a percentage of control values (mean, SEM), during infusion of saline (○) and thiopentone (●). ▲=Mean plasma thiopentone concentrations. Note that the thiopentone infusion rate was doubled after 30 min of infusion.

Table 1 Physiological variables mean (95% confidence interval). MAP=Mean arterial pressure, Pa_{CO_2} and Pa_{O_2}=the arterial carbon dioxide and oxygen tensions, respectively. *$P<0.05$ compared with initial and 30-min values

Variable	Initial value	Value after 30 min	Final value	ANOVA (*P* value)
Pa_{CO_2} (kPa)	4.5 (4.0–5.1)	4.9 (4.4–5.5)	7.5 (6.3–8.7)*	<0.001
Pa_{O_2} (kPa)	11.5 (9.2–13.7)	9.7 (8.8–10.7)	7.1 (6.1–8.0)*	0.002
pH	7.40 (7.37–7.43)	7.36 (7.32–7.40)	7.17 (7.09–7.25)*	0.008
Packed cell volume (%)	44 (40–48)	45 (44–46)	38 (36–40)	0.017
MAP (mm Hg)	126 (117–135)	115 (109–121)	70 (52–88)*	0.001
Rectal temperature (°C)	37.3 (36.7–37.9)	37.5 (37.0–38.0)	35.2 (34.2–35.2)*	0.016

Table 2 hEEG and withdrawal response descriptors of the pharmacodynamics of thiopentone (mean (95% confidence interval)). MWT=Mechanical withdrawal threshold (g). *P* values are for paired Student's *t*-tests comparing results for hEEG end-points with end-points determined from the withdrawal reflex

	Maximal effects (% of control values)		Plasma thiopentone concentration (μg ml^{-1})					
			Maximal effect		Centroid		50% inhibition	
Rat	hEEG Power	1/MWT	hEEG Power	1/MWT	hEEG Power	1/MWT	hEEG Power	1/MWT
STP7	177	150	12	10	28	23	42	38
STP8	181	189	13	12	32	25	42	37
STP9	175	444	20	16	36	29	57	52
STP10	200	166	16	12	39	32	52	52
STP11	240	170	19	16	35	24	57	37
Mean (95% CI)	195 (164–226)	223 (81–365)	16 (12–20)	13 (10–16)	34 (29–39)	27 (23–31)	50 (41–59)	43 (34–52)
CV%	14	55	23	21	13	15	16	19
P value	0.312		0.006		0.001		0.250	

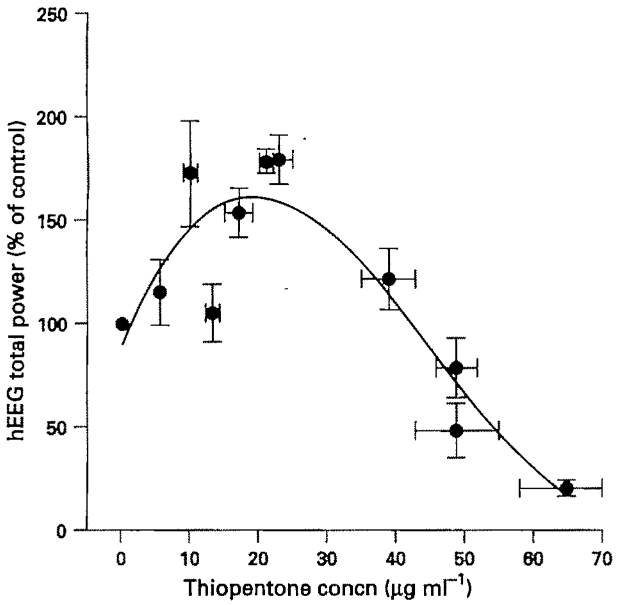

Figure 2 Study 1. Pharmacodynamic relationship between total power of the hippocampal EEG (hEEG) and plasma thiopentone concentrations. The line represents the best fit polynomial regression relationship (P=0.006). Values are mean (SEM).

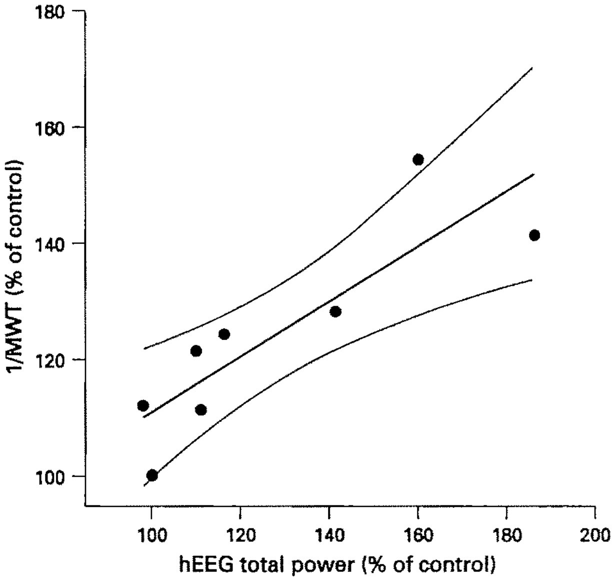

Figure 3 Study 2. Correlation between 1/MWT and total power of the hEEG, both expressed as a percentage of control values (P=0.006). The linear regression line together with its 95% confidence limits is shown.

STUDY 1: INFLUENCE OF THIOPENTONE ON hEEG

The hEEG did not change during infusion of saline. The biphasic effect of infusion of thiopentone on the hEEG is shown in figure 2 (one-way Friedman repeated measures ANOVA on ranks, P<0.001). Total power increased progressively until plasma thiopentone concentrations of 20–30 µg ml^{-1} (75–115 µmol litre^{-1}) were reached. The maximum value of total power was 195 (164–226) % of control, achieved at a mean plasma thiopentone concentration of 16 (10–26) µg ml^{-1} (68, 38–98 µmol litre^{-1}; P=0.008). Total power then decreased progressively to a minimum of 22 (11–33) % (P=0.008 *vs* control) at a thiopentone concentration of 61 (49–72) µg ml^{-1} (231, 185–272 µmol litre^{-1}). Power density (proportion of total power in the three bandwidths examined) did not change during infusion of thiopentone (P=0.42), suggesting that the primary effect of thiopentone infusion was on hEEG amplitude.

The pharmacodynamics of thiopentone with respect to the hEEG and withdrawal response thresholds were characterized by four descriptors (table 2). These descriptors were maximal effect (compared with control) and plasma thiopentone concentrations at maximal effect ($C_P$max), at the centroid ($C_P$centroid) and at the point of 50% inhibition. Comparison of the pharmacodynamic descriptors (table 2) shows that $C_P$max and $C_P$centroid were less for the nocifensive reflex measure of CNS effect than for hEEG total power. This suggests that although both CNS effects show enhancement at plasma thiopentone concentrations in the range 10–20 µg ml^{-1} (38–76 µmol litre^{-1}), the effects on nociception occurred at slightly lower plasma thiopentone concentrations than for hEEG total power. As the effect site kinetics appear to be similar for EEG and nociception,[14] the nocifensive response would appear to be more sensitive to thiopentone than the hEEG response.

STUDY 2: CORRELATION BETWEEN hEEG TOTAL POWER AND NOCIFENSIVE REFLEX THRESHOLD

Over the plasma thiopentone concentration range 0–30 μg ml^{-1} (0–115 μmol $litre^{-1}$), the measures of CNS drug effect, hEEG total power and 1/MWT, expressed as a percentage of control values, increased linearly (ANOVA, F=34, 22, df=7, and P=0.001 and 0.006 for hEEG and 1/MWT, respectively) with drug concentration. hEEG total power was consequently highly correlated with 1/MWT (Pearson product moment coefficient=0.862, P=0.006) (fig. 3).

Discussion

The results of this study showed that subanaesthetic concentrations of thiopentone enhanced hEEG power and reduced nocifensive reflex threshold responses in the same range of plasma concentrations. The pharmacodynamic profiles of these two measures of CNS effect were highly correlated, particularly in the concentration range 0–30 μg ml^{-1} (0–115 μmol $litre^{-1}$) (P=0.006). As the hEEG effects of thiopentone are thought to reflect the concentration of drug at the CNS effect site,[6,9] this finding suggests that nocifensive reflex thresholds are a valid measure of CNS effects for thiopentone. Nocifensive reflex thresholds provide a discrete measure of anaesthetic depth which can be used throughout the entire range of clinically relevant thiopentone concentrations. In contrast, the presence or absence of a withdrawal response to noxious stimulation evaluates the pharmacodynamic relationship at only one behavioural end-point.

Dundee[15] first reported that thiopentone enhanced the response to somatic pain in humans, an effect that was shown to occur also in rodents.[16] Subsequent studies have shown that nocifensive reflexes can be enhanced by a variety of anaesthetics[4,5,13] in a concentration-dependent, time-independent manner,[14] and that the reflex enhancement remains constant under pseudo-steady state conditions.[4,17] Our results agree with the findings of MacIver and colleagues[9] that hEEG amplitude and total power increased with plasma thiopentone concentrations of 15–20 μg ml^{-1} (57–77 μmol $litre^{-1}$). Taken together, these findings support a role for nocifensive reflex threshold measurements in the assessment of the CNS effects of thiopentone. Gustafsson and colleagues[18] have recently quantified the depth of thiopentone anaesthesia in the rat using quantal responses to a variety of stimuli over a large range of pseudo-steady state plasma thiopentone concentrations. The use of the nocifensive reflex threshold enabled us, in this study, to extend their findings through a more detailed examination of the pharmacodynamics of thiopentone within the lowest range of concentrations (0–30 μg ml^{-1} 0–115 μmol $litre^{-1}$).

Previous *in vitro* studies of field potential recordings in the rat hippocampal slice preparation have reported results similar to ours. MacIver and Roth[19] found that pentobarbitone 200–800 μmol $litre^{-1}$ had a biphasic stereospecific effect on excitatory synaptic responses in the hippocampus.

Potential confounding factors in the present study include the use of partial restraint, and the cardiorespiratory effects of thiopentone in spontaneously breathing animals. With the present model, we were previously unable to demonstrate any influence of partial restraint on nocifensive reflex thresholds.[3,14] Although the physiological effects of thiopentone in the later stages of study 1 could clearly have influenced the hEEG and nocifensive thresholds, our main focus was in the initial phase of the infusion, when plasma thiopentone concentrations were less than 30 μg ml^{-1} (113 μmol $litre^{-1}$). All of the animals had normal physiological variables during this phase of the study (table 1), and the shorter infusion strategy used in study 2 did not disturb any of the physiological variables that we measured.

In summary, the results of this study demonstrated the validity of nocifensive reflex thresholds to quantify anaesthetic depth with thiopentone in the plasma concentration range 0–30 μg ml^{-1} (0–115 μmol $litre^{-1}$). Although peak nociceptive effects occurred at slightly lower thiopentone concentrations than peak activation of hEEG, the changes in nocifensive reflex threshold correlated well with changes in total power in the hEEG.

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Effect of extradural analgesia on the paradoxical arousal response of the electroencephalogram

S. KIYAMA AND J. TAKEDA

Summary

Despite widespread recognition of the potential role of the processed electroencephalogram (pEEG) as a monitor of depth of anaesthesia, few studies have examined the effects of surgical stimuli on the intraoperative pEEG. Two groups of gynaecological patients (*n*=10 in each group), with or without pre-incisional extradural analgesia, undergoing gynaecological laparotomy under nitrous oxide and isoflurane anaesthesia were monitored with routine haemodynamic observations and pEEG. Patients who received pre-incisional extradural analgesia showed no significant changes in pEEG variables during surgery (mean spectral edge frequency 95 percentile (SEF95) 13.3 (SD 1.4) Hz), whereas in all patients without pre-incisional extradural analgesia, a significant decrease in SEF95 was noted (6.5 (1.1) Hz after incision compared with a pre-incisional value of 12.5 (1.4) Hz) together with an increase in arterial pressure (paradoxical response). In the latter group, SEF95 and arterial pressure returned to pre-incisional values after extradural analgesia was established during operation. During emergence from anaesthesia, both groups showed a significant increase in SEF95 (25.7 (1.4) Hz). This study suggests that intraoperative pEEG arousal response was different from changes detected when anaesthesia was terminated at the end of surgery. Surgical stimuli in the absence of adequate analgesia induced a paradoxical arousal response. (*Br. J. Anaesth.* 1997; **79**: 750–753).

Key words
Monitoring, electroencephalography. Anaesthesia, depth. Anaesthetic techniques, extradural. Anaesthetics volatile, isoflurane.

The electroencephalogram (EEG) has been used to monitor depth of anaesthesia,[1 2] to titrate i.v. anaesthesia[3 4] or as an index of equipotency when comparing two different types of anaesthetics.[5] Although most previous studies have examined EEG changes while patients are anaesthetized[6] or awakening from anaesthesia,[7–9] few anaesthetists would have difficulty in recognizing whether and when their patients lose or regain consciousness. Therefore, the use of EEG monitoring during these periods may not be necessary. However, it is during the intraoperative period when the difficulty arises in assessing adequacy of anaesthesia, particularly in the presence of neuromuscular block.

Several previous studies identified a threshold value of EEG numerical descriptors to recognize transition from surgical anaesthesia to the pre-arousal state.[1 8] It is therefore tempting to consider that the EEG pattern of imminent arousal, that is a dominant shift to low-amplitude fast waves, also occurs when anaesthesia is inadequate to suppress autonomic responses to noxious stimuli. However, it has been suggested that the mechanisms of arousal during emergence from anaesthesia may differ from arousal reactions induced by noxious stimulation.[10] Consequently, if the EEG is to be used as a routine monitoring tool in the operating theatre, the effects of different anaesthetics and also those of surgical stimuli must be elucidated. There are only a few studies from the same group dealing with the effect of surgery *per se* on intraoperative EEG.[11 12] These investigations showed that in response to surgical incision, a pattern occurs consisting of slow waves with autonomic signs such as an increase in arterial pressure and heart rate,[11] and this response was termed "paradoxical" arousal. Although the underlying mechanisms of this paradoxical EEG response remain unclear, we have shown that pEEG variables returned to pre-incisional values after extradural analgesia.[13] These findings prompted this study, to clarify the effect of extradural analgesia on intraoperative EEG changes, by comparing two groups who received extradural analgesia either before or after surgical incision.

Patients and methods

After obtaining Institutional Review Board approval and verbal informed consent, we studied 20 female ASA I patients undergoing elective total abdominal hysterectomy, allocated randomly to one of two groups of 10 subjects each to receive extradural analgesia either before or after surgical incision.

S. KIYAMA, MD, Department of Anaesthesia, Shizuoka Red Cross Hospital, 8–2, Ohtemachi, Shizuoka 420, Japan. J. TAKEDA, MD, PHD, Department of Anesthesiology, Keio University, School of Medicine, 35 Shinanomachi, Tokyo 160 Japan. Accepted for publication: July 16, 1997.

·Correspondence to S. K.

Patients received ranitidine 150 mg by mouth the night before surgery and again on the morning of surgery. No other sedatives or analgesics were given. Approximately 500 ml of lactated Ringer's solution were infused i.v. before insertion of an extradural catheter. A lumbar extradural catheter was sited at the L2–3 or L3–4 interspace. In both groups, 3 ml of 1% lignocaine with adrenaline 1:200 000 were given via the catheter as a test dose. An additional dose of 1.5% plain lignocaine 20 ml was administered in the pre-incisional extradural group (group 1). Analgesia extending from T4 to the sacral dermatome was confirmed by pinprick before induction. The post-incisional extradural group (group 2) did not receive any further local anaesthetic before induction. Instead, 20 ml of 1.5% plain lignocaine were given immediately after the measurement point at 15 min after incision in group 2.

In both groups, general anaesthesia was induced with thiopentone 5 mg kg^{-1} i.v. followed by inhalation of 1.0% end-tidal isoflurane and nitrous oxide in oxygen (fresh gas flow 5 litre min^{-1}, $F\text{I}_{O_2}$ 0.4). Tracheal intubation was facilitated with vecuronium 0.1 mg kg^{-1} i.v. The lungs were ventilated to maintain end-tidal carbon dioxide concentration at 4.7–5.0 kPa and inhalation anaesthesia was continued as above for the first 30 min after the start of surgery. Anaesthetic gases and carbon dioxide were measured by an anaesthetic gas monitor (Capnomac Ultima, Datex, Helsinki, Finland). Patients were questioned for recall of intraoperative events in the immediate postoperative period and on the following day.

pEEG MEASUREMENT

The pEEG was monitored by a Dräger pEEG monitor (version 3.01; Dräger AG, Lübeck, Germany). Four disposable electrodes in the bilateral fronto-mastoid configuration at the F3-A1 and F4-A2 positions, according to the international 10–20 nomenclature system, and a reference electrode in the frontal midline, were attached using EEG paste (Elefix, Nihon Kohden Corp., Tokyo, Japan), as described previously.[14 15] Impedance of the electrodes were maintained at less than 5 kΩ during the study.

The EEG was recorded at a sampling rate of 128 Hz and an epoch length of 2 s. The raw EEG signal was processed using fast Fourier transform. Processed EEG descriptors, including SEF95, median frequency (MF) and relative power of the delta, theta, alpha and beta bands, and the raw EEG waveform were displayed and recorded on a PC-compatible computer (T100CS, Toshiba, Tokyo, Japan). The pEEG was monitored continuously from induction of anaesthesia to emergence. At the postoperative off-line pEEG analysis, the raw EEG was inspected to ensure that the analysed data were devoid of artefacts caused by the occasional use of surgical diathermy. Data for SEF95, MF and relative power of the four EEG bands were averaged over 10 consecutive artefact-free epochs at the following times: (1) 10 min after tracheal intubation and before incision; (2) 15 min after incision; (3) 30 min after incision; and (4) when patients opened their eyes in response to verbal stimuli.

STATISTICAL ANALYSIS

Patient characteristics were compared using the unpaired *t* test and the Mann–Whitney *U* test, where appropriate. Intra-group comparisons of mean arterial pressure, heart rate and pEEG variables at the four times were analysed using repeated measures analysis of variance (ANOVA). Significant differences found with ANOVA were confirmed by two-sided, paired *t* tests for comparisons over time within groups. Bonferroni's correction for multiple comparisons was applied. Inter-group comparison at each time was performed by unpaired *t* test. $P<0.05$ was considered significant. Statistical calculations were performed using InStat 2.03 for Macintosh (GraphPad Software, San Diego, CA, USA).

Results

The two groups were comparable in age, weight, height, duration of surgery, amount of crystalloid fluid used during anaesthesia and surgical blood loss (table 1). Patients in group 2 showed a significant increase in mean arterial pressure at 15 min after incision, whereas mean arterial pressure in group 1 decreased slightly at 15 and 30 min after incision (table 2). Arterial pressure decreased significantly after extradural analgesia in group 2. There were no significant changes in heart rate in the groups throughout the study.

There were no significant differences in intra-operative SEF95 and MF values compared with pre-incisional values in group 1. In contrast, all patients in group 2 showed a significant decrease in SEF95 and MF after surgical incision (table 3). The relative

Table 1 Patient details (mean (SD) or median (range))

	Group 1 (pre-incisional extradural) ($n=10$)	Group 2 (post-incisional extradural) ($n=10$)
Age (yr)	44 (33–61)	48 (33–63)
Weight (kg)	56 (4)	53 (6)
Height (cm)	156 (4)	154 (4)
Anaesthesia (min)	98 (17)	103 (17)
Surgery (min)	58 (17)	63 (22)
Fluid (ml)	1300 (1000–1800)	1300 (800–1750)
Blood loss (g)	205 (30–390)	250 (20–510)

Table 2 Haemodynamic data (mean (SD)). MAP=Mean arterial pressure, HR=heart rate **$P<0.01$ *vs* group 1; ***$P<0.001$ *vs* group 1; ††$P<0.01$ *vs* 10 min after intubation

	MAP (mm Hg)	HR (beat min^{-1})
Group 1 (pre-incisional extradural)		
10 min after intubation	78 (7)	75 (11)
15 min after incision	69 (8)††	69 (12)
30 min after incision	69 (8)††	67 (9)
Emergence	86 (4)	82 (11)
Group 2 (post-incisional extradural)		
10 min after intubation	87 (6)**	74 (8)
15 min after incision	114 (10)***††	77 (12)
30 min after incision	71 (6)††	70 (7)
Emergence	89 (6)	78 (10)

Table 3 Mean (SD) [95% CI] SEP95 (Hz), MF (Hz) and relative power in each EEG frequency band. ***P<0.001 vs group 1; †††P<0.001 vs 10 min after intubation

	SEF95 (Hz)	MF (Hz)	δ band (%)	θ band (%)	α band (%)	β band (%)
Group 1 (pre-incisional extradural)						
10 min after intubation	13.7 (1.7) [12.5, 14.8]	4.4 (0.7) [3.9, 4.9]	57.1 (8.2) [51.3, 62.9]	20.0 (2.6) [18.1, 21.8]	16.1 (5.5) [12.1, 20.0]	6.7 (2.9) [4.6, 8.7]
15 min after incision	13.4 (1.3) [12.4, 14.3]	4.6 (0.7) [4.1, 5.1]	57.7 (6.4) [53.1, 62.2]	19.1 (4.3) [16.0, 22.2]	16.1 (6.0) [11.8, 20.3]	6.3 (2.0) [4.9, 7.7]
30 min after incision	13.3 (1.5) [12.2, 14.3]	4.6 (0.7) [4.1, 5.1]	57.0 (9.5) [50.2, 63.8]	18.7 (6.7) [13.9, 23.4]	17.6 (4.9) [14.1, 21.0]	5.5 (1.7) [4.3, 6.7]
Emergence	25.4 (1.3) [24.5, 26.3]†††	11.1 (2.5) [9.3, 12.8]†††	30.3 (8.2) [24.4, 36.1]†††	11.5 (10.0) [4.3, 18.6]	12.0 (4.2) [9.0, 15.0]	44.8 (13.0) [35.5, 54.1]†††
Group 2 (post-incisional extradural)						
10 min after intubation	12.5 (1.4) [11.5, 13.5]	4.3 (1.0) [3.6, 5.0]	56.3 (7.9) [50.7, 62.0]	19.2 (5.8) [15.0, 23.3]	19.3 (6.2) [14.8, 23.7]	4.8 (2.3) [3.1, 6.5]
15 min after incision	6.5 (1.1) [5.8, 7.3]***†††	2.6 (0.4) [2.4, 2.9]***†††	90.1 (5.0) [86.5, 93.7]***†††	6.7 (3.7) [4.0, 9.3]***†††	1.6 (0.8) [1.0, 2.2]***†††	1.5 (1.3) [0.5, 2.5]***†††
30 min after incision	12.0 (1.3) [11.1, 12.9]	4.2 (0.8) [3.6, 4.8]	58.9 (7.8) [53.3, 64.5]	19.9 (4.6) [16.6, 23.1]	17.5 (5.9) [13.3, 21.7]	3.5 (2.0) [2.1, 4.8]
Emergence	26.0 (1.5) [24.9, 27.0]†††	11.5 (2.9) [9.4, 13.6]†††	19.3 (6.8) [14.4, 24.1]†††	12.1 (8.0) [6.4, 17.8]	18.4 (9.1) [11.9, 24.9]	50.7 (11.6) [42.4, 58.9]†††

power of the delta band increased significantly while those of the theta, alpha and beta bands decreased significantly at 15 min after incision. SEF95 and MF in these patients returned to pre-incisional value after extradural analgesia. In both groups there were significant increases in SEF95 and MF when patients opened their eyes at the end of surgery compared with intraoperative values. Inter-group differences in SEF95 and MF were significant only at 15 min after incision. A suppression–burst pattern of raw EEG was not observed in any patient throughout the study. At the postoperative interview, no patient reported intraoperative recall.

Discussion

This study is the first to have shown clearly that lack of analgesia is associated with a significant change in pEEG variables. The EEG is a measure of electrical activity, primarily of the cerebral cortex. Therefore, afferent noxious stimuli from the surgical field may be detected as EEG changes whereas effective extradural analgesia interrupts these ascending stimuli. The EEG showed a dominant shift to slow waves after surgical incision in all patients who did not receive pre-incisional extradural analgesia (group 2). This change was accompanied by a significant increase in mean arterial pressure suggesting that depth of anaesthesia was inadequate to suppress sympathetic responses. Therefore, this EEG change may be regarded as paradoxical arousal. In contrast, in patients who received pre-incisional extradural analgesia (group 1), there were no significant changes in pEEG variables, at least for the first 30 min after incision, compared with those before surgery. These results suggest that when analgesia is inadequate, the EEG shifts to low-frequency rather than high-frequency waves which characterize transition from surgical anaesthesia to the arousal state. One may argue that paradoxical arousal after skin incision in group 2 may have been caused by the haemodynamic changes themselves rather than by lack of analgesia. To clarify if haemodynamic changes influence the EEG, another study in which patients without pre-incisional extradural analgesia are given vasodilators or β antagonists to prevent cardiovascular responses after skin incision may be necessary.

Standard EEG monitoring of the international 10–20 system is not readily applicable to routine surgical patients. The EEG monitored using the fronto-mastoidal configuration in this study can be a reasonable compromise in daily clinical practice. However, because of the spatial heterogeneity of EEG activities,[12] it should be noted that the paradoxical arousal response may not be demonstrated clearly when the EEG is monitored in other electrode configurations.

Our findings support those of Bischoff and colleagues' previous report[11] on the paradoxical arousal response. First, in eight of their 10 urological patients, anaesthetized with isoflurane and nitrous oxide, EEG slowing was noted during surgical manipulation with an increase in arterial pressure during steady-state isoflurane anaesthesia with a concentration of only 0.6% during transabdominal urological procedures. This suggests that analgesia was likely to be inadequate when the paradoxical arousal response was recorded. Second, surgical stimuli during open urological and gynaecological procedures are considered to be similar, at least in the initial phase. Although the paradoxical arousal response was clearly identified in both of these procedures, it is not clear if this paradoxical phenomenon occurs in other types of surgery. Third, Bischoff and colleagues recorded the EEG for 20 min. It would be interesting to observe the EEG for longer while the extent of noxious surgical stimuli changes with time. In this study, it could be argued that even without extradural analgesia, this paradoxical response may have disappeared while patients were breathing nitrous oxide and 1.0% isoflurane. However, because of a significant increase in arterial pressure after incision in these patients, which most anaesthetists would treat by giving more analgesics or inhalation anaesthetics, it was considered unethical to maintain a relatively light level of anaesthesia deliberately beyond the

15-min observation period in paralysed patients. In group 1 patients, intraoperative SEF95 was maintained within a relatively narrow range at approximately 13 Hz, whereas in group 2 patients, SEF95 was approximately 12 Hz after extradural analgesia following the paradoxical arousal response. These findings are consistent with previous reports of SEF values during the maintenance phase of anaesthesia.[5,8,16] Although there were no cases of intraoperative awareness in either group, it is unclear if light general anaesthesia reflected by sympathetic hyperactivity and the pEEG paradoxical arousal response lead to intraoperative awareness if not treated correctly.

One of the problems when assessing the pEEG as a monitor of depth of anaesthesia is that a change in pEEG is dependent on the anaesthetic agent used. For example, previous studies on the EEG during sufentanil induction in cardiac patients have shown that the post-induction SEF95 value was much lower than that observed in the present study.[6,17]

A total i.v. technique or combination of light general anaesthesia and regional block enables titration of different components of anaesthesia, that is hypnosis and analgesia. This is advantageous if we can reliably distinguish which component needs to be adjusted in anaesthetized, paralysed patients. Taking into account the aforementioned limitations and our current knowledge of the EEG effects of various drugs and surgical stimuli, the pEEG may still be far from an ideal monitor of anaesthetic depth. However, with the current practice of balanced anaesthesia, it is noteworthy that the presence or absence of extradural analgesia can be recognized by the paradoxical arousal response after surgical incision. Therefore, adequacy of analgesia should also be considered when assessing the intraoperative pEEG.

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Time-frequency spectral analysis of heart rate variability during induction of general anaesthesia

H.-H. HUANG, H.-L. CHAN, P.-L. LIN, C.-P. WU AND C.-H. HUANG

Summary

We have examined the spectral components of heart rate variability (HRV) during induction of anaesthesia with thiopentone, tracheal intubation and subsequent inhalation of isoflurane–nitrous oxide. Commonly used spectral analysis methods such as fast Fourier transformation or autoregressive modelling require stationary data and are not suitable for the rapidly changing HRV data in this period. An advanced spectral analysis method, time-frequency analysis, which can treat non-stationary data, was used in this study. Multiple spectra were generated to demonstrate the time-related spectral components of HRV. Mid-frequency power (MF, 0.08–0.15 Hz), high-frequency power (HF, 0.15–0.5 Hz) and MF/HF ratio at baseline, after induction (before intubation), immediately after intubation and during maintenance periods were calculated and compared. MF and HF powers decreased after induction and were reduced further in the maintenance period but MF/HF ratio remained unchanged after induction. Immediately after intubation MF and HF powers did not differ significantly from the immediate pre-intubation values, but MF/HF ratio did. (*Br. J. Anaesth.* 1997; **79**: 754–758).

Key words
Anaesthetics i.v., thiopentone. Anaesthesia, general. Anaesthetics volatile, isoflurane. Heart, heart rate. Measurement techniques, spectral analysis.

Spectral analysis of heart rate variability (HRV) provides a non-invasive means of assessing the regulation of the autonomic nervous system.[1–4] The power spectrum of HRV is quantified usually by the spectral power within the frequency intervals of high frequency (HF, 0.15–0.5 Hz), mid frequency (MF, 0.08–0.15 Hz) and low frequency (LF, 0.02–0.08 Hz). HF power is related to respiratory effect and affected mainly by parasympathetic regulation. MF power is related to baroreflex activity and is controlled by both sympathetic and parasympathetic nervous systems. LF power is considered to have some relationship to thermoregulation or renin–angiotensin system functions.[1] Spectral analysis of HRV has been used in several clinical investigations, such as prediction of the prognosis of myocardial infarction patients[5 6] and assessment of autonomic status of diabetic patients.[7] Several recent reports have focused on the change in spectral components of HRV during anaesthesia by different methods.[8–13] In many of these studies, the power spectrum of HRV was calculated by fast Fourier transformation (FFT) or autoregressive modelling (AR).[14] However, the assumption of data stationarity cannot be met in some situations. During induction of general anaesthesia, rapid onset of anaesthetic action, effect of tracheal intubation and administration of inhalation agents cause rapid changes in autonomic activity in a short period of time. It is not feasible to obtain stable data in such a short time period for conventional spectral analysis methods under this circumstance. Few studies have investigated the continuous change in spectral components of HRV and the possible effects of the various events during anaesthesia.

Time-frequency spectral analysis is an advanced spectral analysis method[15] which can generate multiple spectra with time instead of a single spectrum for the whole data segment, as is the case with the FFT method. In addition, time-frequency spectral analysis based on the so called "quadratic time-frequency distribution" can provide good resolution in both time and frequency. It has been used widely for time-varying signal analysis in many applications and should be a suitable tool for studying the time-related spectral components of HRV during induction of anaesthesia.

In this study, time-frequency spectral analysis was used to obtain continuous spectral components of HRV during induction of general anaesthesia. The changes in the spectral components of HRV during different stages of anaesthesia were compared quantitatively.

HUI-HSUN HUANG, MD, Department of Anaesthesiology, National Taiwan University Hospital, 7 Chung-Shan South Road, Taipei, Taiwan and Department of Electrical Engineering, National Taiwan University, 1 Roosevelt Road Sec.4, Taipei, Taiwan. HSIAO- LUNG CHAN, PHD, Department of Electrical Engineering, Hwa Hsia College of Technology and Commerce, Taipei, Taiwan. PEI-LIN LIN, MD, CHI-HSIANG HUANG, MD, Department of Anaesthesiology, National Taiwan University Hospital, 7 Chung-Shan South Road, Taipei, Taiwan. CHIEN-PING WU, Department of Electrical Engineering, National Taiwan University, 1 Roosevelt Road Sec. 4, Taipei, Taiwan.
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Correspondence to C.-H. H.

Patients and methods

The study was approved by the institutional Ethics Committee and informed consent was obtained from all patients. We studied 30 adult patients, ASA I or II, undergoing various types of elective surgery. None had cardiovascular, pulmonary, neurological, diabetic or thyroid disease. No premedication was given before surgery. In the operating room, ECG, non-invasive arterial pressure and pulse oximetry were monitored (Hewlett Packard Model 78354A, Hewlett Packard Corp., Palo Alto, CA, USA), and concentrations of end-tidal carbon dioxide and anaesthetic agent were analysed using a gas analyser (Capnomac, Datex Corp., Finland). General anaesthesia was induced with thiopentone 5 mg kg^{-1}, fentanyl 2 $\mu g\ kg^{-1}$, droperidol 0.05 mg kg^{-1} and suxamethonium 2 mg kg^{-1}, followed by tracheal intubation. Anaesthesia was maintained with isoflurane and 50% nitrous oxide in oxygen. The concentration of isoflurane was initially 2% and maintained at 1% expiratory concentration after the wash-in phase. Neuromuscular block was maintained with atracurium after tracheal intubation. The lungs were ventilated mechanically at a rate of 10 bpm and tidal volume was set to maintain end-tidal carbon dioxide tension at 4.0–4.6 kPa.

DATA MANAGEMENT

ECG monitoring was started at least 5 min before induction of anaesthesia. ECG data were recorded and digitized onto a personal computer via analogue to digital conversion at a sampling rate of 500 Hz. The recording ended at approximately 20 min after tracheal intubation, before the start of surgery. The recorded data were used for off-line analysis. Detection of peaks of R waves and R-R interval sequence calculation were performed by software using threshold and slope detection combined with rejection of candidate peaks during estimated refractory periods. ECG waveforms were displayed on the screen with detected peaks marked, and visual verification and manual editing were performed. The cardiac tachogram, which indicates instantaneous heart rate along a time axis, was calculated from the R-R interval series and was re-sampled at a frequency of 2 Hz to obtain an even sampling sequence.[16] Before time-frequency analysis, the data sequence was de-trended by polynomial fitting. There are many methods in time-frequency analysis, and the smoothed pseudo Wigner–Ville distribution (SPWVD) was used in this study. The power spectrum based on SPWVD for a specific time is calculated by the data within a time interval before and after that specific time. The length of the interval is termed the "window length". The "correlation" is calculated at each time and summed by applying different weights to each time point. The weight decreases as the distance from the specific time increases. The result is transformed into frequency domain to obtain the power spectrum. The window length was 64 s in our study. The power spectra were generated at 4-s intervals. A technical appendix is attached to this article to provide a brief description of the algorithm used. Readers who are interested in more of the theory and implementation of SPWVD time-frequency analysis are referred to the literature.[15 17 18]

The spectral power of each spectrum was calculated at high frequency (HF, 0.15–0.5 Hz), mid frequency (MF, 0.08–0.15 Hz) and low frequency (LF, 0.02–0.08 Hz). Spectral powers were averaged in 2-min intervals for the following four periods: (1) baseline: from 2 min before induction to the start of induction; (2) pre-intubation or post-induction: from 2 min before tracheal intubation to the time of tracheal intubation. The patient was under the effect of the induction agents during this period; (3) immediately post-intubation: from the start of tracheal intubation to 2 min later; and (4) maintenance phase: from 10 min after tracheal intubation to 2 min later when the patient was already anaesthetized with isoflurane. The average spectral power of HRV in each period was performed on 30 consecutive spectra. In addition, the ratio of MF to HF power and mean heart rate in each period were also calculated.

All of the above ECG data management tasks, except manual verification of R wave peaks, were performed by software developed by ourselves with the computer language C (Borland C++ 3.1, Borland International Inc., CA, USA). Time-frequency analysis was performed by MATLAB (MathWorks Inc., MA, USA) on the Microsoft operating system Windows 3.1 (Microsoft Co., USA).

Comparisons of HRV data between the four periods were carried out using one-way repeated measures ANOVA with the Student–Neuman–Keuls test using the commercial package SigmaStat for Windows version 1.0 (Jandel Co., USA) run on the Microsoft operating system Windows 3.1. The significance level was set at $P<0.05$.

Results

The cardiac tachogram of one patient with a typical pattern is shown in figure 1A. The typical tachogram indicates a transient increase in heart rate during tracheal intubation and a gradual decrease after intubation. In figure 1B, the time-related spectral components of HRV are demonstrated by the three-dimensional plots of these spectra *vs* time. This is a typical time-frequency pattern of HRV with the change in spectral components in response to various events of anaesthesia. There are two points to be noted in the interpretation of such types of plots. (1) The frequency range less than 0.08 Hz, the lower limit of the MF range, is the low frequency (LF) range. For the short period used in this study, LF powers are generated mainly from the trends in mean heart rates and the powers are highest around the time of tracheal intubation because heart rate undergoes maximal change during this period. Although LF powers are usually higher than MF or HF powers, it was not our concern in this study and it should not be confused with MF or HF powers. (2) The spectral powers are calculated by integration of all amplitudes over the relative frequency ranges

Table 1 Heart rate variability (HRV) data for baseline, post-induction, immediate post-intubation and maintenance periods. All data are mean (SEM). *Significant *vs* baseline. †Significant *vs* post-induction; all $P<0.05$

	MF ((beat min^{-1})^2)	HF ((beat min^{-1})^2)	MF/HF	HR (beat min^{-1})
Baseline	2.10 (0.46)	1.23 (0.17)	1.57 (0.19)	85.2 (2.6)
Post-induction	1.13 (0.34)*	0.49 (0.08)*	1.95 (0.29)	88.5 (2.3)
Immediate post-intubation	0.99 (0.21)*	0.33 (0.05)*	3.14 (0.31)*†	99.2 (2.4)*†
Maintenance	0.07 (0.01)*†	0.13 (0.02)*†	0.62 (0.10)*†	72.8 (2.2)*†

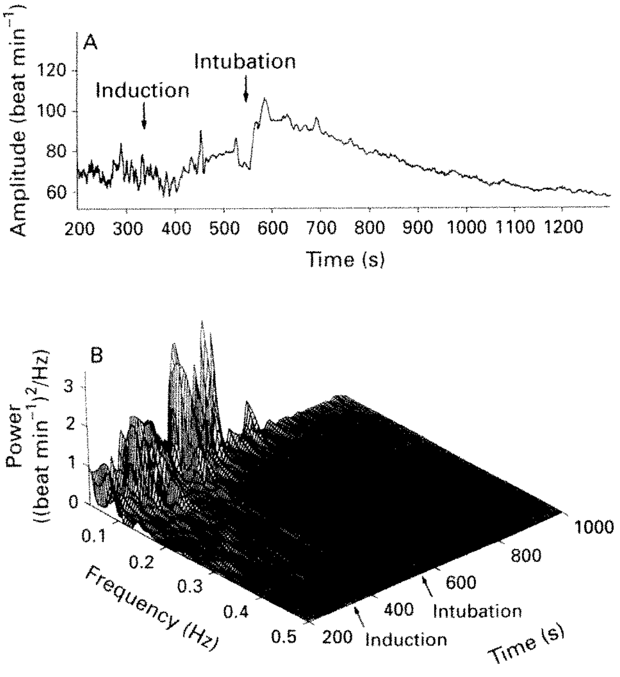

Figure 1 A: Cardiac tachogram of one patient with a typical pattern during induction of general anaesthesia. The unit of the tachogram in beat min^{-1}. B: Three-dimensional plot of multiple spectra generated by time-frequency analysis of heart rate variability (HRV) along the time axis. Note the frequency of MF power is 0.08–0.15 Hz and HF power is 0.15–0.5 Hz.

rather than counting only the highest peaks. The existence of one or several very high peaks in a single spectrum does not necessarily imply that the spectrum has higher powers than other spectra. This makes visual interpretation of the three-dimensional plots only qualitative rather than quantitative, and accurate powers must be calculated from the raw data.

In the three-dimensional plot in figure 1B, there are apparent spectral powers in MF and HF ranges before induction (baseline period). MF spectral power slowly decreased after the induction agents were given and tracheal intubation was performed. It decreased further after administration of inhalation agents. HF spectral power exhibited a similar trend as MF spectral power but it is not clear from the three-dimensional plots because of its low amplitude compared with MF spectral power.

Averaged MF and HF powers, MF/HF ratio and mean heart rate in different periods are shown in table 1 and figure 2. Both MF and HF powers decreased significantly after induction, remained at the same level immediately after tracheal intubation but decreased significantly in the maintenance phase. MF/HF ratio did not change significantly after induction. It increased immediately after tracheal intubation and decreased to a lower than baseline level in the maintenance phase during inhalation anaesthesia. Mean heart rate exhibited a similar trend as MF/HF ratio.

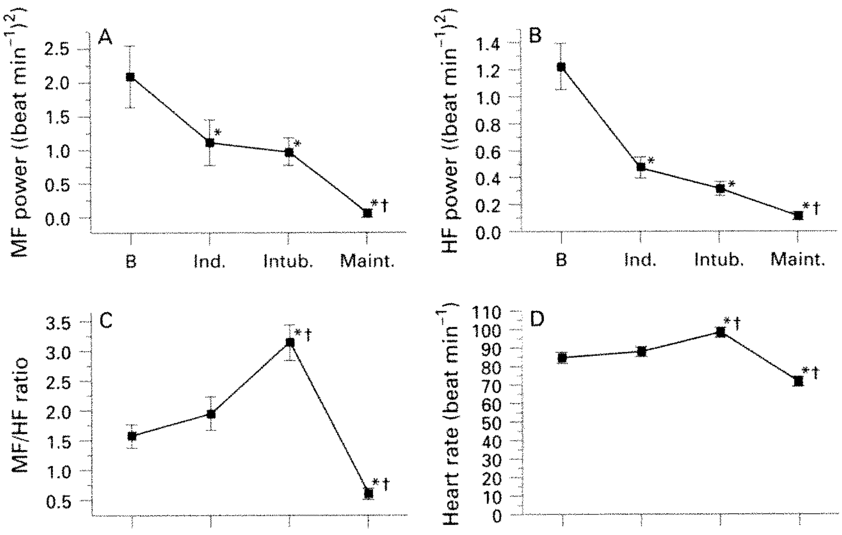

Figure 2 Plot of heart rate variability (HRV) data at baseline (B), after induction (Ind.), immediately after intubation (Intub.) and during the maintenance periods (Maint.). A=MF power, B=HF power, C=MF/HF ratio and D=mean heart rate. All data are mean (SEM). $P<0.05$ compared with: *baseline; †after induction.

Discussion

The spectral powers of MF and HF in heart rate signals are usually modulated by the sympathetic and parasympathetic nervous systems, and the ratio of MF to HF is often used as an index for autonomic nervous system balance. These components of spectral power of HRV can be used as indices of changes in autonomic activity during various types of anaesthesia and many researchers have focused on them. The commonly used methods in these investigations are FFT and AR modelling, which have the advantages of easy implementation and fast computation. The preliminary assumption of FFT or AR modelling is data stationarity, which implies that the data must be "stable" during the observation period.[14] When this condition is not met, the calculated spectral power is not reliable. The autonomic nervous system activity and HRV signals change rapidly during induction of anaesthesia, especially immediately before and after tracheal intubation. Spectral analysis by FFT or AR models is limited in interpreting data in this period because the assumption of data stationarity cannot be verified easily. Because of this, analysis of this transient period, which is most important for observation of the effect of tracheal intubation, remained largely ignored in previous studies.

In the time-frequency spectral analysis method, calculation of power spectra is based on correlation-like terms, which implicitly considers the temporal relationship of the data. This makes the assumption of data stationarity unnecessary. Analysis of the transient period immediately before and after tracheal intubation becomes possible and reliable. Based on time-frequency analysis, our study showed an increase in MF/HF ratio immediately after tracheal intubation. There was also a small but significant increase in heart rate but no significant increase in MF power. Because the MF/HF ratio is usually regarded as an index of the balance between the sympathetic and parasympathetic systems, these results suggest that autonomic nervous system balance is the main factor affected by tracheal intubation with induction agents. MF/HF ratio is more sensitive than MF power as an indicator of sympathetic nervous system activation. The increase in MF/HF ratio and mean heart rate immediately after intubation indicates that sympathetic nervous system activation after intubation was not blocked totally by the induction agents. Our result is similar to that of Hopf and colleagues who concluded that MF/HF ratio rather than MF power (LF in their article) reflects sympathetic activity during extradural anaesthesia.[19]

Because the time-frequency analysis method can generate multiple spectra continuously, we can also observe the change in HRV during different time segments in the induction phase. In our study, both MF and HF powers were reduced dramatically after administration of the induction agents. This confirms that the fluctuations in heart beat are suppressed by induction agents, as reported by others.[8–10] MF/HF ratio increased slightly but not significantly during induction which suggests that the balance of the autonomic nervous system was not altered to any great extent by the induction agents.

Several studies have demonstrated reductions in MF and HF powers by isoflurane.[11–13] In our study, MF and HF powers and MF/HF ratio in the maintenance phase were not only lower than those at baseline, but also lower than those in the post-induction phase. In the beginning of the maintenance phase, alteration of HRV could be the result of the combined effects of induction and inhalation agents. However, the data we used for statistical comparison were obtained 10 min after tracheal intubation and the pharmacological effect of the short-acting agents we used such as thiopentone may be very low. Hence, it is likely that the change in MF and HF powers in the maintenance phase was caused mainly by the inhalation agents. The effect of isoflurane on HRV is more profound than the combination of our i.v. induction agents. Ireland and colleagues have shown that HRV recovered promptly after patients could follow verbal commands during recovery from general anaesthesia.[20] There is little information on the duration of effect of thiopentone on HRV, and therefore we do not know if the effect on HRV disappears immediately or decreases after thiopentone redistributes.

FFT or AR modelling methods also suffer from the balance between temporal resolution and frequency resolution. In contrast, the time-frequency analysis method implicitly takes different data length for different frequency ranges in the signal and maintains both time and frequency resolution. Because of this and the advantages described above, the time-frequency method has been applied in many clinical fields,[21] including analysis of HRV in response to postural change and pharmacological effects,[17 22] and detection of brain activity in the EEG.[23 24] Our study is another example of the application of the time-frequency method. This new method not only increases temporal and spatial resolutions, but also opens some new windows. Time-frequency analysis should be very useful for other clinical studies on the interpretation of rapidly changing signals.

Appendix

The outline of the time-frequency analysis method used in our study is described below. Most of the descriptions make reference to the literature.[15 17 18] Interested readers should consult the original articles for further details.

The time-frequency analysis method is a class of signal processing algorithm which was developed under rigorous mathematical theory.[18] Wigner–Ville distribution (WVD) is one of the most commonly used in this class. The discrete version of the WVD of a time series $x(n)$ is defined as:

$$W(n,f)=\frac{1}{2}N\sum_{k=-N+1}^{N-1} x(n-k)x(n+k)\,e^{-2\pi kf/N}$$

Practically, n in the above formula is usually time and f=frequency, and the WVD is a function of time and frequency The term "distribution" has a similar meaning to "function".

The above formula is exactly the Fourier transformation of $x(n-k)x(n+k)$ on the variable k, so the WVD can be implemented by the FFT algorithm with only additional multiplications The major difference between the WVD and conventional discrete Fourier transformation (DFT) is that in WVD the correlation-like term $x(n-k)x(n+k)$ is transformed, rather than $x(n)$ itself in the DFT. If there is a rapid changing component in the original data, the time scale of the component is short and the correlation term decays rapidly to negligible values. This makes the effective time window length of a rapid changing component short. In contrast, a slow varying component keeps its correlation term non-negligible for a longer time. Thus the WVD implicitly uses different time window lengths for different frequencies in the data and keeps both time resolution and frequency resolution and can treat rapid time-varying signals.

The use of the correlation terms in the above formula could produce spurious spectral peaks and smearing in the time or frequency axis. Two modifications are made to solve the problems. The first is the use of a so called analytical signal, which is a signal without negative frequencies. Let $X(k)$ be the DFT of $x(n)$. We keep the positive frequency part of $X(k)$ and set its negative frequency part to zero:

$$Z(k)=2X(k)\ k>0,$$
$$Z(k)=X(k)\ k=0,$$
$$Z(k)=0\ k<0.$$

The inverse DFT of this $Z(k)$ is the analytical signal of the original signal $x(n)$, and is denoted $z(n)$. This $z(n)$ is used instead of $x(n)$ to obtain better results.

The second modification is the introduction of two window functions in the transformation:

$$W(n,f)=\frac{1}{2}N\sum_{k=-N+1}^{N-1}|h(k)|^2\left[\sum_{p=-M+1}^{M-1}g(p)z(n+p-k)z^*(n+p+k)\right]e^{-2\pi jkf/N}$$

The window $g[p]$ is termed the time smoothing window and the window $h[k]$ is the frequency smoothing window; z^* is the complex conjugate of z. The above formula is the final form of SPWVD. The time smoothing window and frequency smoothing window suppress spurious peaks and largely improve the quality of the spectrum.

The commonly used $g[p]$ is the unit rectangular window, or $g[p]=1$ (this is different from not using any window at all unless M is also set as 1). The commonly used $h[k]$ is a Gaussian window, defined as

$$h(k)=e^{-1/2[\alpha k/(N/2)]^2}\quad 0\leq|k|\leq N/2$$

In our study, the original data $x(n)$ is the R-R interval series. Analytical signal $z(n)$ is computed and used in the formula of SPWVD. Window functions of $g(p)=1$, $M=9$, and $\alpha=2.5$ and $N=64$ for Gaussian window $h(k)$ are used. For every specific n, the resulted $W(n,f)$ represents one single spectrum on the frequency axis f. The value of n is increased by 8 at every step, which means one spectrum is produced for every 4 s of data. In the three-dimensional plots, the time axis is n, the frequency axis is f and the values of $W(n,f)$ are plotted on the vertical axis. The spectral powers are calculated by the integration of $W(n,f)$ values.

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Assessment of a new ventricular contractile index obtained with transoesophageal echocardiography before and after cardiopulmonary bypass in cardiac surgical patients

M. KIKURA, T. IKEDA, T. OHNUMA AND K. IKEDA

Summary

We have compared a new contractile index "left ventricular end-systolic wall stress–heart rate-corrected velocity of circumferential fibre shortening (vcfc)" with conventional contractile indices in 13 patients undergoing coronary artery bypass grafting. We generated the slopes of the "end-systolic wall stress–vcfc", "end-systolic wall stress–area" and "peak arterial pressure–area" relationships by altering arterial pressure before and after cardiopulmonary bypass (CPB). In all patients, significant correlations were obtained for end-systolic wall stress–area and peak arterial pressure–area relationships before and after CPB. In all patients, significant inverse linear correlations were obtained for the end-systolic wall stress–vcfc relationship before CPB; however, inverse linear correlation was absent in eight patients after CPB. It may be that the increased afterload had less influence on left ventricular systolic function after CPB as a possible mechanism of loss of the inverse linear correlation in the end-systolic wall stress–vcfc relationship. (*Br. J. Anaesth.* 1997; **79**: 759–765).

Key words
Surgery, cardiovascular. Heart, cardiopulmonary bypass. Heart, contractility. Monitoring, transoesophageal echocardiography.

The left ventricular pressure–volume relation developed by Suga and Sagawa has been used widely as a contractile index that is relatively insensitive to loading conditions,[1–3] and clinical use of this method has been reported for assessment of ventricular function in cardiac surgical patients.[4–6] The pressure–volume relationship requires invasive techniques to construct left ventricular pressure–volume loops and acute alteration of loading conditions by vena cava occlusion to obtain the end-systolic pressure–volume relationship. A relatively less invasive technique is available by examining the slope of the left ventricular end-systolic wall stress–dimension relationship by echocardiography. This relationship is based on the concept of the pressure–volume relationship, and is constructed by manipulating arterial pressure with vasoactive agents.[7 8] The end-systolic wall stress–dimension relationship correlates linearly within the physiological range and is sensitive to the inotropic state.[7 8]

Recently, a new echocardiographic assessment of contractility became available by examining the relationship between left ventricular end-systolic wall stress and heart rate-corrected velocity of circumferential fibre shortening (*v*cfc).[9] The slope of the end-systolic wall stress–*v*cfc relationship was found to be inversely linear over a wide physiological range, relatively independent of preload and sensitive to changes in contractility.[9 10] In the analysis of this relationship, an upward shift of the slope indicates an increased inotropic state, and a downward shift of the slope indicates a depressed contractile state.[9 10] Although the left ventricular end-systolic wall stress–*v*cfc relationship appears to be useful for assessment of ventricular contractility,[9–11] there is no information on this contractile index in cardiac surgical patients. Accordingly, we compared the left ventricular end-systolic wall stress–*v*cfc relationship with the conventional end-systolic wall stress–area and peak arterial pressure–area relationships before and after cardiopulmonary bypass (CPB) in patients undergoing coronary artery bypass grafting.

Patients and methods

After obtaining approval from the Department of Medical Ethics Committee and informed consent, we studied 13 patients undergoing elective primary coronary artery bypass grafting. Patients with an ejection fraction of less than 45%, previous history of myocardial infarction, regional wall motion abnormalities (diagnosed as severe hypokinesis, akinesis, dyskinesis or aneurysmal), valvular disease or congenital heart disease diagnosed by previous cardiac angiographic or echocardiographic examination were excluded. Also excluded were patients with atrial fibrillation or any oesophageal or gastric

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MUTSUHITO KIKURA, MD, TAKEHIKO IKEDA, MD, TETSURO OHNUMA, MD, KAZUYUKI IKEDA, MD, FRCA, Department of Anaesthesiology and Intensive Care, Hamamatsu University School of Medicine, 3600 Handa-cho, Hamamatsu, Japan 431-31. Accepted for publication: July 30, 1997.

Correspondence to M. K.

pathology diagnosed as a contraindication to transoesophageal echocardiography.

Anaesthesia was induced with fentanyl 10 μg kg^{-1}, diazepam 0.15–0.2 mg kg^{-1} and vecuronium 0.15 mg kg^{-1}, and maintained with high-dose fentanyl (up to a total dose of 60 μg kg^{-1}) supplemented with benzodiazepines (diazepam or midazolam, or both) and 1–1.5% sevoflurane. Vecuronium was given to facilitate mechanical ventilation with 60% oxygen in air before CPB, or 100% oxygen after CPB. All patients were monitored with leads II and V5 of the electrocardiogram, and with radial and pulmonary artery catheters. After tracheal intubation, a gastroscope tipped with a 5-MHz multi-plane transoesophageal ultrasonic transducer (Hewlett Packard, Andover, MA, USA) was inserted into the oesophagus and positioned behind the left ventricle to obtain a short axis view at the level of the midpapillary muscles. The transducer was connected to an ultrasonograph (Sonos 1500, Hewlett Packard, Andover, MA, USA). While arterial pressure and heart rate were being recorded, two-dimensional echocardiograms were recorded on S-VHS videotapes by the attending anaesthetists (M. K., T. I. and T. O.) with at least 3 yr experience with intraoperative transoesophageal echocardiography.

After pericardiotomy, before aortic and right atrium cannulations, haemodynamic and echocardiographic data were obtained. Cardiac output was measured during apnoea at the end of expiration, in duplicate, by the thermodilution technique with 10 ml of iced saline at 0 °C using a pulmonary artery catheter (Opticath with Oximetrix 3 50130, Abbott Lab., North Chicago, IL, USA). Any cardiac output measurement significantly different (greater than ±10%) from its pair was excluded, and a repeat measurement was obtained. Peak systolic arterial pressure was adjusted to 90–110 mm Hg, as the baseline value, by continuous infusion of phenylephrine or prostaglandin E_1 (PGE_1), or both. To generate the slopes of the contractile indices, peak systolic arterial pressure, measured by a radial artery catheter, was increased to 30% of baseline by continuous infusion of phenylephrine 0.5–2.0 mg kg^{-1} min^{-1}, and then decreased to baseline by continuous infusion of PGE_1 0.05–0.2 mg kg^{-1} min^{-1}. Arterial pressure was recorded continuously on a multichannel recorder (78576A, Hewlett Packard, Andover, MA, USA) at a paper speed of 25 mm s^{-1}, and two-dimensional echocardiograms of the left ventricular short axis view with an electrocardiogram lead II were recorded on videotape while haemodynamic data were recorded simultaneously. We synchronized the video and the strip chart recorder to match the pressure values with the echocardiograms. All haemodynamic measurements were made during the expiratory pause phase of the ventilator cycle. Haemodynamic indices were calculated from pressure and cardiac output data with the use of standard formulae.[12]

CPB was conducted using a Cobe CML membrane oxygenator with a non-pulsatile flow of 2.2 litre min^{-1} m^{-2}. The system was primed with 1500 ml of balanced salt solution, 150 ml of 15% mannitol and hetastarch 500 ml. In all patients, hypothermia (25–28 °C) and aortic cross-clamping with cold hyperkalaemic cardioplegia were used. After the primary surgical operation, patients were warmed to a bladder temperature of 36.5–37 °C. The heart was defibrillated after cardiac reperfusion if sinus rhythm did not resume spontaneously. As a pressure gradient between central aortic pressure and radial artery pressure was often observed (sometimes more than 15–20 mm Hg) before weaning from CPB, femoral arterial pressure was monitored routinely to estimate central aortic pressure rather than radial artery pressure. A significant aortic-to-radial artery pressure gradient has been reported during and after CPB in a previous study[13] and femoral arterial pressure reproduces central aortic pressure more reliably than radial arterial pressure after CPB.[14] Patients were weaned from CPB using dopamine 5–8 μg kg^{-1} min^{-1} or nitroglycerin 0.5–1.0 μg kg^{-1} min^{-1}, or both, started before weaning to achieve a systolic arterial pressure >90 mm Hg and pulmonary capillary wedge pressure (PCWP) ≤18 mm Hg. Left ventricular preload was assessed by PCWP and left ventricular cavity area. After completion of CPB and protamine administration, measurements were repeated after aortic and right atrium decannulations but before sternal closure if patients were haemodynamically stable without new regional wall motion abnormalities. During manipulation of arterial pressure, the rates of i.v. volume infusion and continuous infusion of dopamine 5–8 μg kg^{-1} min^{-1} were kept constant, and bolus administration of i.v. anaesthetic drug was not performed. Sevoflurane was not used in any patient after weaning from CPB.

TRANSOESOPHAGEAL ECHOCARDIOGRAPHIC ANALYSIS

Echocardiographic analysis was performed by off-line tracings with the Hewlett Packard Sonos 1500 ultrasonograph system. Images were analysed by the authors (M. K., T. I. and T. O.) with previous published experience in the analysis of ventricular function.[11 15–17] We identified at least 10 data points at end-expiration for each regression line to generate the slopes of contractile indices in each patient. We traced the left ventricular short-axis endocardium at end-diastole to obtain end-diastolic area (EDA) and end-diastolic circumference (EDC). We traced endocardium and epicardium at end-systole to obtain end-systolic area (ESA) with papillary muscles included, end-systolic circumference of endocardium (ESC), and total area (At) enclosed by the left ventricular epicardium and right side of the septum. Leading-edge to leading-edge methods were used to trace the endocardium and epicardium.[18] Left ventricular ejection time (LVET) was determined using the number of frames (one every 33 ms) from end-diastole to end-systole. We identified ventricular end-diastole by the peak of the R wave and end-systole by the minimal left ventricular dimension. Fractional area change (FAC) and systolic circumferential fibre shortening (CFS) were determined as follows[19]:

$$\text{FAC}\ (\%) = 100 \times (\text{EDA} - \text{ESA})\ /\ \text{EDA}$$
$$\text{CFS}\ (\%) = 100 \times (\text{EDC} - \text{ESC})\ /\ \text{EDC}$$

We determined *vcfc* and end-systolic wall stress (index of afterload) as follows[9 20]:

$$vcfc = \text{CFS}\ (\%) \times (\text{RR})^{1/2}\ /\ (\text{LVET} \times 100)$$

where RR=interval between cardiac cycles, measured as the number of frames from the peak of the R wave to the next peak of the R wave, and EDC and ESC are measured in centimetres.

$$\text{End-systolic wall stress} = (1.35 \times P\text{sys} \times \text{ESA})/(\text{At} - \text{ESA})$$

where end-systolic wall stress is measured in g cm^{-2}, *P*sys=peak systolic arterial pressure (mm Hg), At and ESA are measured in cm^2 and 1.35 is a factor to convert mm Hg to g cm^{-2}. Each parameter of area in this equation was obtained with two-dimensional echocardiography. For practical convenience with M-mode echocardiogram, this original equation has been modified to one with endocardial diameter and wall thickness[20] However, two-dimensional echocardiography may involve less error to estimate wall stress than does M-mode echocardiogram. We used peak systolic arterial pressure in our calculation for end-systolic wall stress, based on the methods of Reichek and colleagues, indicating that end-systolic wall stress with peak systolic arterial pressure correlated well with invasively measured wall stress in a variety of clinical conditions.[7]

STATISTICAL ANALYSIS

One- and two-way analysis of variance followed by the Bonferroni multiple comparison test were used to compare changes in haemodynamic and echocardiographic data before and after CPB, and changes in those data during manipulation of arterial pressure.

In each patient, we plotted end-systolic wall stress on the *X*-axis against *vcfc* on the *Y*-axis, and plotted end-systolic area on the *X*-axis against end-systolic wall stress or peak arterial pressure on the *Y*-axis. At least 10 data points were plotted to generate each regression line in each patient. The linear regression equation was calculated by simple linear regression analysis with the least squares method. Statistical analysis was conducted using statistical software (Statview 4.0, Super ANOVA, Abacus Concept, Inc., Berkeley, CA, USA). $P<0.05$ was considered statistically significant, and all data are expressed as mean (SD).

Results

The heart was in sinus rhythm in all patients, and no new regional wall motion abnormalities, ST-segment changes or arrhythmias were observed. In these patients, a short axis view was obtained satisfactorily and echocardiographic analysis was performed. Three patients received two bypass grafts (one internal mammary artery and one saphenous vein), and 10 patients received three bypass grafts (one internal mammary artery and two saphenous veins). Patient data are given in table 1. Haemodynamic and echocardiographic variables before and after CPB are summarized in table 2. Heart rate and cardiac index after CPB were significantly higher than those before CPB, and systemic vascular resistance index after CPB was significantly lower than that before CPB. There was no significant difference in any other haemodynamic or echocardiographic variables between before and after CPB. Arterial pressure increased significantly from 107 (14)/52 (5) (72 (5)) to 142 (12)/65 (6) (90 (5)) mm Hg with phenylephrine administration, and then decreased to 107 (13)/53 (5) (73 (4)) mm Hg

Table 1 Patient characteristics (mean SD or range) or number) (*n*=13)

Age (yr)	62 (52–74)
Sex (M/F)	10/3
Weight (kg)	55.6 (12.0)
Height (cm)	158.2 (9.7)
Body surface area (m^2)	1.6 (0.2)
Cross-clamp time (min)	75 (15)
Cardiopulmonary bypass time (min)	140 (26)

Table 2 Haemodynamic and echocardiographic data before (Pre-) and after (Post-) cardiopulmonary bypass (CPB) (mean (SD)). AP=Arterial pressure, PAP=pulmonary artery pressure, PCWP=pulmonary capillary wedge pressure, CVP=central venous pressure, CI=cardiac index, SVI=stroke volume index, SVRI=systemic vascular resistance index, PVRI=pulmonary vascular resistance index, FAC=fractional area change, *vcfc*=heart rate-corrected velocity of circumferential fibre shortening, ESWS=end-systolic wall stress, EDA=end-diastolic area, ESA=end-systolic area. $^*P<0.05$ compared with Pre-CPB

	Pre-CPB (*n*=13)	Post-CPB (*n*=13)
Heart rate (beat min^{-1})	65 (12)	97 (7)*
AP (mm Hg)	107 (14)/52 (5) (72 (5))	98 (8)/47 (5) (65 (4))
PAP (mm Hg)	24 (5)/12 (3) (17 (4))	29 (6)/15 (5) (20 (5))
PCWP (mm Hg)	11 (4)	13 (4)
CVP (mm Hg)	9 (4)	8 (4)
CI (litre $\text{min}^{-1}\ \text{m}^{-2}$)	2.4 (0.5)	3.2 (0.5)*
SVI (ml $\text{beat}^{-1}\ \text{m}^{-2}$)	38 (11)	33 (7)
SVRI (dyn s $\text{cm}^{-1}\ \text{m}^2$)	2372 (569)	1481 (323)*
PVRI (dyn s $\text{cm}^{-5}\ \text{m}^2$)	208 (64)	196 (86)
FAC (%)	52.5 (10.0)	54.9 (14.0)
vcfc (circ s^{-1})	0.712 (0.249)	0.769 (0.323)
ESWS (g cm^{-2})	46.9 (21.6)	36.4 (11.2)
EDA (cm^2)	12.8 (3.6)	12.1 (2.3)
ESA (cm^2)	6.2 (2.5)	5.7 (1.9)

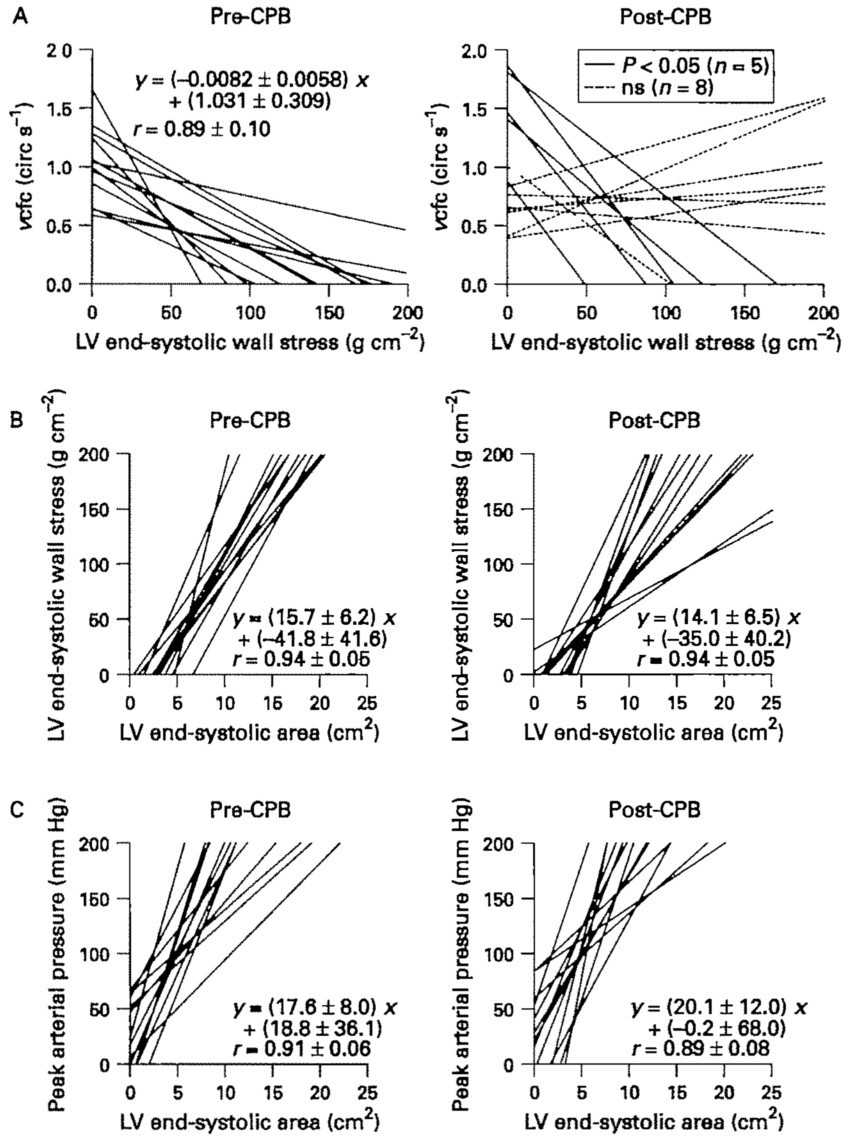

Figure 1 For the left ventricular (LV) end-systolic wall stress–heart rate-corrected velocity of circumferential fibre shortening (*vcfc*) relationship (A), significant inversely linear correlations were obtained in all patients before cardiopulmonary bypass (Pre-CPB), but the correlations were no longer inversely linear in eight patients (broken lines) after CPB (Post-CBP). For the LV end-systolic wall stress–area (B) and peak arterial pressure–area (C) relationships, significant linear correlations were obtained in all patients before and after CPB. ns=not significant.

with administration of PGE$_1$ before CPB, and increased significantly from 98 (8)/47 (5) (65 (4)) to 130 (11)/62 (5) (83 (5)) mm Hg after administration of phenylephrine, and then decreased to 101 (12)/50 (4) (67 (4)) mm Hg after administration of PGE$_1$ after CPB. During alteration of afterload, there was no significant change in EDA (index of left ventricular preload) before CPB (12.4 (3.3) cm^2 at baseline, 13.2 (3.8) cm^2 after administration of phenylephrine and 12.6 (3.7) cm^2 after PGE$_1$), or after CPB (11.9 (2.3) cm^2 at baseline, 13.1 (2.8) cm^2 after phenylephrine and 12.2 (2.5) cm^2 after PGE$_1$), and there was no significant difference in EDA in each state between before and after CPB. Manipulation of arterial pressure was accomplished within 15–20 min in all patients.

For the echocardiographic data, 292 data points were obtained for regression analysis; 146 data points before CPB and 146 data points after CPB. Regression equations, correlation coefficients, and lines between end-systolic wall stress and *vcfc*, between end-systolic wall stress and area, and between peak pressure and area are illustrated in figure 1. In all patients, the relationships between end-systolic wall stress and area, and between peak arterial pressure and area, showed significant linear correlations before and after CPB. Significant inverse linear correlations were obtained between end-systolic wall stress and *vcfc* before CPB in all patients, but the correlation was lost in eight patients after CPB. Between measurements taken before and after CPB, there was no significant difference in ventricular contractility measured by the slopes of the end-systolic wall stress–area and peak pressure–area relationships.

During alteration in arterial pressure, left ventricular end-systolic wall stress increased significantly after administration of phenylephrine and then returned to baseline after PGE$_1$ administration before and after CPB (fig. 2A). Between before and after

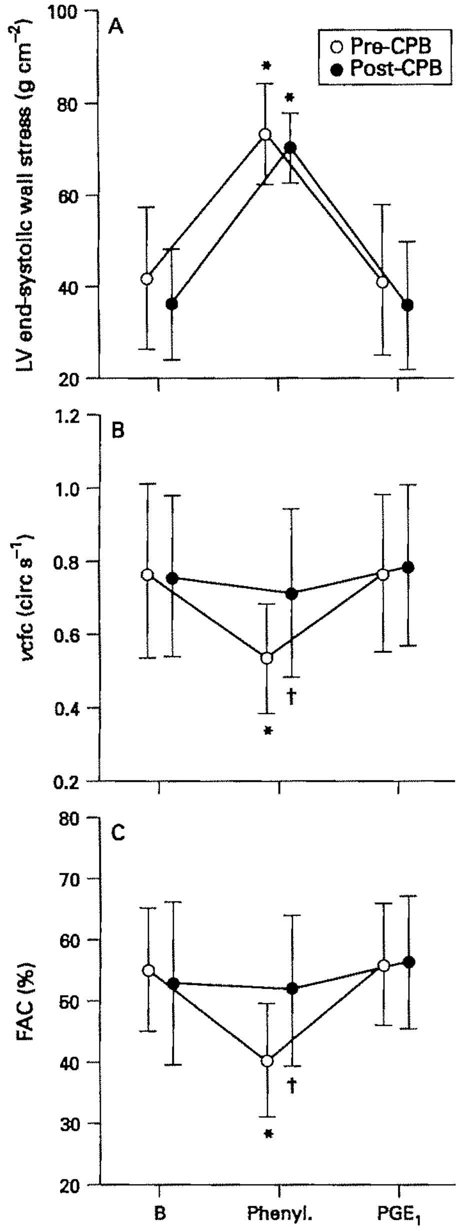

Figure 2 Changes in left ventricular (LV) end-systolic wall stress (A), heart rate-corrected velocity of circumferential fibre shortening (*vcfc*) (B) and fractional area change (FAC) (C) at baseline, after administration of phenylephrine (Phenyl.) and after administration of prostaglandin E_1 (PGE_1) before and after cardiopulmonary bypass (CPB). $P<0.05$ compared with: *baseline; †after CPB.

CPB, there was no significant difference in arterial pressure or end-systolic wall stress at baseline, after administration of phenylephrine or after administration of PGE_1. *vcfc* and FAC decreased significantly when end-systolic wall stress increased significantly before CPB, but there were no significant changes in *vcfc* or FAC after CPB (fig. 2B, 2C). Between patients with an inverse linear correlation ($n=5$) and those without an inverse linear correlation ($n=8$) in the end-systolic wall stress–*vcfc* relationship, there was no significant difference in aortic cross-clamp time (76 (15) *vs* 75 (15) min), CPB time (135 (35) *vs* 143 (21) min), dopamine requirements (7.2 (1.0) *vs* 7.5 (1.0) μg kg^{-1} min^{-1}), left ventricular EDA (11.9 (2.0) *vs* 12.3 (1.9) cm^2) or *vcfc* (0.748 (0.236) *vs* 0.726 (0.230) circ s^{-1}), respectively.

Discussion

The results of this study indicate that, in patients undergoing coronary artery bypass grafting, assessment of ventricular contractility is possible by examining the slope of the end-systolic wall stress–*vcfc* relationship and the end-systolic wall stress–area and peak arterial pressure–area relationships before CPB. After CPB, assessment of the contractile state is possible by measurements of the slope of the end-systolic wall stress–area and peak arterial pressure–area relationships, but not the slope of the end-systolic wall stress–*vcfc* relationship because of loss of the inverse linear correlation. It is possible that increased afterload had less influence on left ventricular systolic function after CPB as a possible mechanism for the loss of the inverse linear correlation between end-systolic wall stress and *vcfc*.

The end-systolic wall stress–*vcfc* relationship reported by Colan, Borow and Neumann[9] is based on the force–velocity relationship found in isolated human papillary muscle.[21] Although several studies have examined a contractile state by using the end-systolic wall stress–*vcfc* relationship,[9–11] there is no report on this contractile index in cardiac surgical patients. In this study, the significant influence of afterload on *vcfc* and FAC observed before CPB was not detected after CPB, and the significant inverse linear correlations between end-systolic wall stress and *vcfc* observed in all patients before CPB were lost after CPB. Although both *vcfc* and FAC are known to be dependent on left ventricular afterload,[9] the afterload dependence of *vcfc* and FAC observed in individual subjects before CPB was not necessarily reproducible after CPB in this study. A possible explanation could be that there was inotropic support with catecholamines during the period after CPB. Beta-receptor stimulation induced by administration of dopamine after CPB might have preserved left ventricular systolic function when afterload increased, although pure alpha adrenergic stimulation by phenylephrine caused significant reductions in ventricular function before CPB. Bolus administration of phenylephrine to patients with coronary artery disease has been shown to cause transient impairment of left ventricular function associated with a severe increase in afterload, while this transient reduction in ventricular function has not been observed in response to bolus administration of noradrenaline (alpha- and beta-receptor agonist).[22] The other possible explanation could be intrinsic beta-receptor stimulation induced by an increase in sympathetic nerve activity in the heart after CPB. An intense sympathomimetic stimulus to the heart was observed at the end of CPB in cardiac surgical patients,[23] and rewarming at the end of CPB markedly increased sympathetic nerve activity in animal experiments.[24]

The left ventricular end-systolic pressure–volume relationship has been established as a contractile index that is relatively insensitive to loading conditions.[1–3] Recently, Gorcsan and colleagues reported less invasive methods to construct pressure–volume loops during inferior vena caval occlusion by using automated echocardiographic measurements of left ventricular cavity area and femoral arterial pressure monitoring.[5 6] Their studies indicated that on-line pressure–area relationships may be clinically useful for estimating ventricular contractility in cardiac surgical patients. The slope of the left ventricular end-systolic wall stress–dimension relationship is also sensitive to the inotropic state.[7 8] The end-systolic wall stress–dimension relationship can be determined by manipulating arterial pressure with vasoactive agents, and is correlated linearly within the physiological range.[7 8] O'Kelly and colleagues reported that the slope of the end-systolic wall stress–dimension relationship obtained before surgical incision was useful for measuring ventricular contractility in patients undergoing coronary artery bypass grafting.[25] To our knowledge, our study is the first to examine if the end-systolic wall stress–dimension relationship is useful for assessment of a contractile state after weaning from CPB. In contrast with the end-systolic wall stress–*v*cfc relationship, our study indicated that the end-systolic wall stress–area and peak arterial pressure–area relationships were useful for assessment of contractile state both before and after CPB. The curvilinearity in a pressure–volume relation has been reported to produce negative values for the extrapolated area–axis intercepts derived from linear regression analysis.[26] The negative area–axis intercept in the peak arterial pressure–area and end-systolic wall stress–area relationships observed in this study might be attributable to such curvilinearity. Wall stress may be a better index of afterload than left ventricular pressure when left ventricular wall thickness is chronically altered, as in ventricular hypertrophy.[27]

We used PGE_1 to decrease arterial pressure. In a previous animal study, we showed that PGE_1 decreased preload and afterload during 10%, 20% and 30% decreases in mean arterial pressure, but had no inotropic action on myocardial contractility assessed by a load-independent contractile index.[16] PGE_1 did not induce significant change in right ventricular contractile state assessed by preload recruitable stroke work as a load-insensitive index in patients after pulmonary resection.[28] Changes in EDA by two-dimensional echocardiography are considered to reflect changes in end-diastolic volume, reflecting a change in LV preload.[29] The absence of significant change in EDA during alteration in afterload indicated that left ventricular preload was affected minimally by afterload manipulations caused by phenylephrine or PGE_1. The absence of significant difference in EDA before and after CPB indicated that left ventricular preload conditions were comparable between those states.

An automated border detection system using integrated backscatter imaging (Acoustic quantification, Hewlett Packard, Andover, MA, USA) is useful for real-time measurements of left ventricular cavity area and circumference by identifying ventricular endocardial–blood boundaries.[30] As determination of wall stress required a tracing of epicardium that was not currently available by automated border detection, time-consuming off-line analysis was necessary in this study.

In summary, determining the slope of the end-systolic wall stress–area and the peak pressure–area relationships permits assessment of ventricular contractility, whereas determining the slope of the end-systolic wall stress–*v*cfc relationship permits assessment of the contractile state before, but not after, CPB, because of the loss of inverse linear correlation.

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Heat retention using passive systems during anaesthesia: comparison of two plastic wraps, one with reflective properties†

S. DEACOCK AND A. HOLDCROFT

Summary

Hypothermia during prolonged surgery may be prevented by active and passive warming methods. We have compared randomly two types of occlusive body wraps in groups of 20 patients. One wrap had additional reflective properties which, by reducing radiative in addition to convective and evaporative heat loss, was expected to improve heat conservation. Patients were studied during hepatopancreatobiliary surgery and both groups were similar in characteristics. Skin and core body temperatures increased and core temperature exceeded 37 °C in 40% of patients in both groups. This continuous increase in temperature was unexpected and the observed heat gain may have been stimulated endogenously by the type of surgery rather than that supplied externally. Overall, mean hourly heat gain was similar in both groups: 71 (SD 28) kJ h^{-1} in the reflective group and 67 (33) kJ h^{-1} in the other group. (*Br. J. Anaesth.* 1997; **79**: 766–769).

Key words

Temperature, body. Temperature, monitoring. Equipment, warming devices. Monitoring, temperature.

Core body temperature in conscious humans is regulated precisely by an intrinsic system with central hypothalamic control and a behavioural system which allows extremes of temperature to be tolerated without hypothermia or hyperthermia developing. Heat is tolerated less than cold because denaturation of proteins occurs at core body temperatures greater than 42 °C whereas a similar decrease in body temperature usually causes reversible changes. Anaesthesia and surgery prevent behavioural responses and alter the homeostatic response to temperature variations by changes in both the cardiovascular effector system and central and peripheral nervous system control.[1] Perioperative core body temperatures therefore often decrease below normal. This iatrogenic hypothermia is associated with numerous postoperative complications of which the most important are shivering, which induces hypoxaemia,[2] and prolongation of drug action.[3] These problems are more common during prolonged surgery, especially when major blood loss occurs and patients are malnourished. In severely ill patients, additional hazards of hypothermia include impaired coagulation[4] and negative postoperative nitrogen balance.[5]

Although the hypothermic effects of anaesthesia on temperature homeostasis may be unavoidable, the physical factors which contribute to heat loss and gain may be controlled. Many different active and passive systems provide heat gain and also prevent heat loss. Body cavity exposure during surgery with resultant evaporative heat loss may not be controllable, but it is possible with access to the body for heat transfer by conduction, convection and radiation. Radiation is considered to be the major source of heat loss in an awake, resting individual. It becomes a significant factor for heat loss during surgery if the patient is uncovered in cold surroundings or is vasodilated.[6] Radiative heat losses can be restricted by the use of metallized plastic foil, such as space blankets, but the increased risk of burns and electric shock has limited their use in the operating theatre, except for specially designed plastic wraps with punctate metal fragments on a plastic backing which do not conduct electricity (Thermadrape; Vital Signs, Sussex, UK).

It was hypothesized that the combination of plastic wraps incorporating a reflective surface to prevent radiative heat loss should provide more heat retention than a simple plastic bag during major surgery. Reflective wraps in volunteers not undergoing surgery or anaesthesia provided better insulation than plastic bags,[7] but reflective blankets during surgery required a large surface area to be covered in order to significantly increase core temperature.[8] It was considered that for ethical reasons relating to the complications of inducing mild hypothermia, unnecessary heat loss should be prevented in this study. Therefore, reflective and ordinary plastic bags were used with standardized heat retentive procedures. Such procedures were known to reduce but not prevent heat loss during major surgery.

S. DEACOCK*, MB BS, DA, FRCA, A. HOLDCROFT, MB CHB, MD, FRCA, Department of Anaesthesia, Royal Postgraduate Medical School and Hammersmith Hospital, Du Cane Road, London W12 0HS. Accepted for publication: July 18, 1997.

*Present address: Department of Anaesthesia, Royal Hampshire County Hospital, Romsey Road, Winchester, Hampshire SO22 5DG.

Correspondence to A. H.

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Patients and methods

After obtaining Ethics Committee approval and informed verbal consent, we studied 40 patients undergoing hepatopancreatobiliary surgery. Patients were allocated by random number tables before the study to one of two groups: in one group the Thermadrape wrap was used and in the other, large, thin transparent plastic bags were used. These wraps covered all limbs, except for i.v. sites. Before anaesthesia all patients were normothermic, and antibiotics were administered routinely for prophylaxis when anaesthesia commenced. The anaesthetic technique was standardized using thiopentone, fentanyl and vecuronium in appropriate doses. After tracheal intubation, anaesthesia was maintained with intermittent positive pressure ventilation of the lungs via a heat and moisture exchanger (Pall) using isoflurane and nitrous oxide in oxygen. Additional analgesia was provided with fentanyl 1 μg kg^{-1} h^{-1} either i.v. or combined with 0.1% bupivacaine and administered extradurally, as indicated clinically. Blood replacement during surgery was given to prevent hypotension and to maintain a packed cell volume of 30–35%. Whole or plasma-reduced blood and albumin solution (4.5% HAS) were infused on a volume replacement basis. The main replacement solution was crystalloid, and Haemaccel was administered as indicated. Urine output was measured every 30 min.

Patients were transferred to theatre from the anaesthetic room, after insertion of invasive monitors for measurement of arterial and venous blood pressures. Active conduction of heat was standardized: a warm air mattress at 39.5 °C was positioned under the patient, fluids were warmed to 36 °C and the ambient theatre temperature was maintained at 21–24 °C. Before surgery the temperature monitors and limb wraps were positioned. Core temperature was measured in the nasopharynx. Four skin temperatures were recorded from the nipple, upper outer arm, mid-dorsal thigh and lateral surface of the mid-calf to provide a calculation for mean skin temperature applicable to anaesthesia.[9] The instrument used was an Ellab PD85U thermometer (Ellab Instruments, Copenhagen). Mean body temperature was measured from core and mean skin temperatures, and from this, using an average value for the specific heat of tissues and the patient's body weight, total body heat was calculated.[10] Hourly temperature measurements were started just before surgery and calculations of total body heat were made every hour during surgery. Change in total body heat was measured from the first record. The relative humidity inside the wraps was measured with a humidity meter (HM humidity and temperature meter, Vaisala, Finland).

A mixed model analysis of variance (using the statistical package, Genstat; NAG Ltd, Oxford, UK) was used to compare the relationship between change in body heat with time in patients wrapped in Thermadrape or plastic bags. The normality assumption of residuals from the ANOVA was checked using the Watson test, and Bartlett's test was used to test the equal variance assumption. In two patients in each group, core body temperature increased to greater than 37.5 °C during surgery. At this time active heating was discontinued and data after this intervention were not included in the statistical analysis.

Results

The two groups were similar in age, body mass index (kg m^{-2}) and duration of operation (table 1). Patient age, height, weight or body mass index did not correlate with the rate of heat gain. Three patients in the Thermadrape group and two in the plastic bag group received extradural infusions. Mean blood loss measured on swabs was 1620 (range 720–13674) ml in the Thermadrape group and 1786 (571–3893) ml in the plastic group.

Mean core temperatures before surgery were 35.8 and 35.8 °C, which increased to 37.3 and 37.2 °C in those patients studied after 7 h of surgery (an increase of 1.5 and 1.4 °C) in the Thermadrape and plastic groups, respectively. Individual core temperatures indicated that 40% of patients in both groups exceeded a value of 37 °C during surgery. Figure 1 shows mean hourly measurements of core body temperature. As the mean duration of surgery was approximately 5 h, confidence intervals became wider after this time.

Mean heat gain was 71 (SD 28) kJ h^{-1} and 67 (33) kJ h^{-1} in the Thermadrape and plastic bag groups,

Table 1 Patients characteristics and duration of operation in the two groups of patients, one wrapped in Thermadrape and the other in plastic bags (mean (SD or range))

	Thermadrape (n=20)	Plastic (n=20)
Age (yr)	52 (28–71)	51 (26–73)
Weight (kg)	72 (11)	72 (11)
Height (m)	1.7 (0.8)	1.7 (0 1)
BMI (kg m^{-2})	25 (3 8)	25 (2.8)
Duration of operation(min)	311 (122)	284 (92)

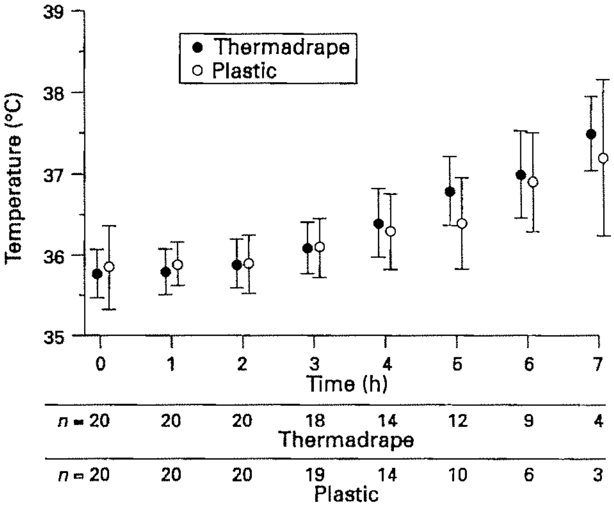

Figure 1 Relationship between core body temperature and duration of surgery for the Thermadrape and plastic bag groups, with hourly values of temperature measured as mean (95% confidence intervals). The number of patients in each group per hour is shown for each full hour of surgery.

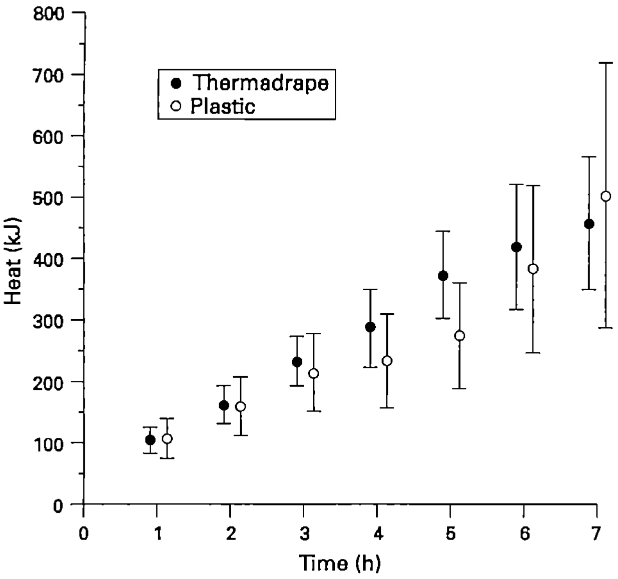

Figure 2 Relationship between cumulative increase in body heat (i.e. difference between heat stored in the patient before surgery and body heat calculated hourly) and duration of surgery for the Thermadrape and plastic bag groups, measured as mean (95% confidence intervals).

respectively. Cumulative mean hourly increases in body heat during surgery are shown in figure 2. There was no significant difference between the two groups for each hour. However, the mixed model analysis of variance demonstrated that there was a significant difference in the relationship between heat gain and time with the two wraps. It appears from figure 2 that heat gain was similar for the first 3 h but then twice as much heat was gained in the next 2 h in the Thermadrape group. This relationship then changed so that patients in plastic wraps gained more than twice as much body heat as in the other group. However, the number of patients studied after 5 h became too few to allow statistical comparison. There were no differences in relative humidity within the wraps during the study; the internal environment inside all wraps reached full saturation within minutes and this was maintained throughout surgery.

Discussion

We expected that hypothermia would be prevented in one of the groups, but instead uninterrupted heat gain was observed in both groups. On induction of anaesthesia, redistribution of body heat normally occurs from the warm core to the cooler peripheral tissues which is followed by a slow, almost linear, decrease in core temperature resulting from heat loss exceeding production. After approximately 3–4 h of anaesthesia, core temperature has been observed to plateau as a result of thermoregulatory vasoconstriction sequestering metabolic heat in the core thermal compartment.[11] General anaesthesia may alter cardiovascular effector control systems of temperature regulation, and in addition may blunt the nervous system response to deviations from normal body temperatures.[1] Widening of the set points at which effector responses for heat gain and loss are generated has been described in patients not undergoing surgery.[12] In effect, this implies that a higher or lower temperature must be reached in order to switch on the respective regulatory response.

No patient was pyrexial before surgery and patients with treated infections were not recruited. This study was undertaken in patients who had major upper abdominal surgery, some of whom had biliary stents with the potential to act as a nidus for infection and the development of septicaemia. Surgery itself induced major haemorrhage but even with blood warmers set at 36 °C this would not have increased body temperature above normal. Another contributing factor to the universal heat gain could have been the thermogenic effects of infused fluids such as albumin solution[13] but it was considered that the amounts used as replacement for blood loss would be inadequate to provide the additional heat generated.

The inclusion of five of 40 patients with extradural infusions requires comment because extradural anaesthesia with segmental block is known to induce peripheral vasodilatation with associated heat loss during surgery[14] or in volunteers.[15] However, a low-dose bupivacaine extradural infusion was used in combination with an opioid for analgesia and a dense segmental block was not achieved. If any effect on body heat was expected, it should have reduced the heat gain observed.

The physical size of the patient did not correlate with the rate of heat gain. This finding did not confirm those in volunteers using insulated drapes whereby the amount of skin covered was an important factor.[7] It was expected that patients with a large surface area related to the limbs would have a different rate of heat flux than those with small limbs, particularly as the wraps were applied in these areas. Body weight, height and body mass index showed no relationship with heat gain.

If heat loss occurs mainly by radiation during anaesthesia and surgery, then the reflective wraps should have prevented major heat loss and this group should have gained heat faster. As this did not occur, radiation as a source of heat loss during surgery may not be a major factor. However, after 3 h of surgery the increase in body heat varied between the plastic and reflective wraps. This could indicate a different response to heat dissipation between the two groups and may account for the comfort felt when wearing the reflective wrap. The relative humidity inside both wraps reached 100% within minutes and hence both wraps effectively prevented evaporative heat loss. The reflective wraps also contained a cotton lining and were produced originally as a comfortable garment to wear. This additional absorptive quality of the reflective wrap may have assisted thermoregulatory evaporation to proceed when body temperature exceeded normal limits.

It was disturbing to observe an increase in core body temperature above normal in both groups as additional methods of active heat transfer could have been used clinically in addition to the ones chosen. Core temperature measurement is usually the only site of body temperature measurement during clinical anaesthesia. However, an increase in total body heat cannot be assumed unless peripheral temperatures are also increased, because in major surgery vasoconstriction may occur with a reduction in blood flow to the skin such that body heat is diverted from the periphery to the centre. The result is that total body heat can decrease while core temperature increases. This may accompany haemorrhagic shock, but was not observed during this study despite major haemorrhage.

Both systems of wraps for heat retention during surgery were effective in preventing heat loss when combined with routinely used methods. An increase in heat gain above heat loss was recorded in all patients during prolonged surgery. This emphasizes the importance of temperature monitoring when active and passive warming measures are used.

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Comparison of the accuracy of the lithium dilution technique with the thermodilution technique for measurement of cardiac output

T. Kurita, K. Morita, S. Kato, M. Kikura, M. Horie and K. Ikeda

Summary

A new indicator dilution technique for measurement of cardiac output is described. Lithium chloride is injected via a central venous catheter and its dilution curve measured in arterial blood using a lithium-selective electrode. We assessed the lithium dilution cardiac output measurement (LiDCO) and a conventional thermodilution cardiac output measurement (ThDCO) by comparing the results of both with cardiac output determined by electromagnetic flowmetry (EMCO) under controlled laboratory conditions in 10 swine. They were monitored with a pulmonary artery catheter, femoral artery catheter and electromagnetic flowmeter placed around the ascending aorta. LiDCO, ThDCO and EMCO measurements were determined at baseline, in a hyperdynamic state produced by administration of dobutamine, at a second baseline and finally in a hypodynamic state induced by propranolol during deep anaesthesia. Data were analysed by linear regression analysis and the comparison method described by Bland and Altman; bias and precision of both LiDCO and ThDCO compared with EMCO were calculated by the method of Sheiner and Beal. The correlation coefficient between LiDCO and EMCO (0.95) was higher than that between ThDCO and EMCO (0.87). The precision value of LiDCO (0.04) was significantly less (i.e. better) than that of ThDCO (0.09). The results of this study indicated that LiDCO was more reliable compared with conventional ThDCO. (*Br. J. Anaesth.* 1997; **79**: 770–775).

Key words
Heart, cardiac output. Measurement techniques, thermodilution. Measurement techniques, lithium dilution. Measurement techniques, flowmetry. Measurement techniques, cardiac output. Pig.

The thermodilution technique using a pulmonary artery catheter has been widely used clinically for measurement of cardiac output. With this technique, insertion of a pulmonary artery catheter involves an invasive procedure associated with several risks and complications.[1–3] A recent report indicated that pulmonary artery catheterization is associated with an increase in mortality and cost of care.[4] Errors in measurement may be introduced by rewarming of the injectate caused by handling before injection and by heat transfer during passage through the pulmonary artery catheter.[5–9] Thermodilution may overestimate cardiac output during a low cardiac output state, probably because of excessive heat exchange secondary to slow passage of injectate.[10 11] A less invasive method is available using a lithium dilution technique that uses lithium chloride as the indicator. A preliminary clinical study of this technique has been reported by Linton, Band and Haire.[12] Lithium chloride, injected into the right atrium via a central venous catheter, is measured by a sensor attached to the peripheral arterial catheter, and cardiac output can be measured without a pulmonary artery catheter. Lithium does not normally exist in the human body, does not bind to plasma or tissue proteins and is excreted almost entirely in urine.[13–15] There have been no studies comparing the lithium dilution technique with the thermodilution technique under controlled hypodynamic or hyperdynamic laboratory conditions. Accordingly, we assessed the reliability of lithium dilution and thermodilution techniques by comparing both with cardiac output determined by electromagnetic flowmetry under controlled hypodynamic and hyperdynamic states.

Materials and methods

EXPERIMENTAL PROCEDURE

After obtaining approval from the Institutional Ethics Committee, we studied 10 swine (body weight 10–15.5 kg). After administration of ketamine 5–7 mg kg^{-1} i.m., general anaesthesia was induced by inhalation of 4% sevoflurane in oxygen 5 litre min^{-1} using a standard animal mask. After induction, the trachea was intubated with a cuffed tracheal tube, and anaesthesia was maintained with 3% end-tidal sevoflurane and 100% oxygen with mechanical ventilation (Harvard apparatus dual phase control pump, GI3, South Natick, MA, USA). A peripheral venous cannula (20-gauge) was

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Tadayoshi Kurita, md, Koji Morita, phd, Shigeru Kato, md, Mutsuhito Kikura, md, Masao Horie, bsc, Kazuyuki Ikeda, md, frca, Department of Anaesthesiology and Intensive Care, Hamamatsu University School of Medicine, 3600 Handa-cho, Hamamatsu, 431-31, Japan. Accepted for publication: August 6, 1997.

Correspondence to T. K.

inserted in the dorsal ear vein and lactated Ringer's solution was infused at a rate of 10 ml kg^{-1} h^{-1}. After induction, vecuronium or pancuronium was administered. End-tidal carbon dioxide was maintained at 4.7–5.3 kPa. Lead II of the electrocardiogram (ECG) was monitored with subcutaneous electrodes introduced into the legs. After median sternotomy and pericardiotomy, the probe of an electromagnetic flowmeter (Electromagnetic blood flowmeter, MFV3200, Nihon Kohden, Tokyo, Japan) was placed around the ascending aorta for continuous measurement of cardiac output. The probe attachment size was varied in order to fit the diameter of each particular aorta (FB120T, FB130T, FB140T, FB150T, FB160T, lumen diameter ranges 12–16 mm, Nihon Kohden). The electromagnetic flowmeter system was calibrated initially and before each change in haemodynamic state. The position of the probe of the electromagnetic flowmeter was checked after the swine was killed with potassium chloride i.v. under deep anaesthesia with 5% inspired sevoflurane.

A pulmonary artery catheter (5 F, 4 lumen, Nihon Kohden) was inserted into the right jugular vein, and a double-lumen catheter (16–18-gauge) was placed in the femoral artery. Arterial pressure was monitored via one lumen of the femoral artery catheter, and blood samples were obtained from the other lumen for measurement of plasma concentrations of lithium. Heparin 100 u. kg^{-1} was administrated in order to avoid blood clotting on the membrane surface of the lithium sensors, thus avoiding deterioration of the sensors. By warming with heating lamps, blood temperature of the swine was maintained in the range 36.5–37.5 °C. In all experiments it took less than 1.5 h from induction of anaesthesia to the first baseline measurements. After baseline measurements were obtained, haemodynamic status was changed from baseline to a hyperdynamic state (20–40% increase in cardiac output monitored with EMCO) by continuous infusion of dobutamine at a rate of 10 μg kg^{-1} min^{-1}, and then returned to baseline. Next, the status was changed from baseline to a hypodynamic state (20–40% decrease in cardiac output) by administration of propranolol 0.5–2.0 mg and increase in end-tidal sevoflurane concentration to 4–5%. After obtaining haemodynamic stability for at least 10 min, cardiac output was measured. ThDCO was determined by a thermodilution computer (Cardiac Output Computer, MTC6210, Nihon Kohden) using 5 ml of ice-cold 5% glucose injected into the right atrium. During apnoea at the end of expiration, indicators for LiDCO and ThDCO were administered by the same person. During measurement of cardiac output, we maintained the i.v. infusion rate constant. Values of EMCO were recorded when the indicators were injected. Measurement of cardiac output was duplicated, and two paired measurements of cardiac output were made in each animal under each haemodynamic condition. Any cardiac output measurement significantly different (greater than ±10%) from its pair was excluded, and a repeat measurement was obtained.

LITHIUM DILUTION CARDIAC OUTPUT MEASUREMENT

A prototype LiDCO measurement system was used (LiDCO, Ltd., London, UK). The lithium sensor consists of a flow-through cell containing a lithium-selective electrode developed for this use.[12] The indicator is lithium chloride 0.15 mol $litre^{-1}$, prepared in glass ampoules by the pharmacy at St Thomas's Hospital (London, UK). The voltage from the sensor is logarithmically related to plasma lithium concentration and is recorded via an electrically isolated preamplifier and analogue to digital converter by a Macintosh computer (PowerBook 5300CS, Apple Computer, Cupertino, CA, USA). Before they were used the sensors were calibrated by exposure to saline and then to a solution of lithium chloride 1 mmol $litre^{-1}$ in saline and recording the change in voltage. A roller pump (CP-136, Nissho Corporation, Osaka, Japan) was used to regulate blood flow from the femoral arterial catheter via the flow-through cell to 4 ml min^{-1} until a stable baseline voltage was recorded. Then, during apnoea at the end of expiration, 0.67 ml of a lithium chloride solution (0.15 mol $litre^{-1}$) was injected (dose=0.1 mmol) as a bolus into the right atrium via the atrial port of the pulmonary artery catheter. The same investigator performed all injections. To ensure that the injection bolus dose was exactly 0.67 ml, the deadspace of this catheter (0.39 ml) had previously been filled with more than 0.4 ml of lithium chloride solution until a small amount of indicator leakage had come out from the tip of the catheter, and had a small peak appeared on the recording curve of the concentration–time course. The primary circulation curve was discriminated from the secondary (or recirculation) curve by the method of Linton, Linton and Band, based on the theory of using a log-normal analysis to determine the integral of the primary curve.[16] Cardiac output was then calculated using the following formula by Linton, Band and Haire[12]:

$$\text{Cardiac output (litre min}^{-1}) = [\text{dose of lithium chloride (mmol)} \times 60] \,/\, [\text{area under curve (mmol litre}^{-1}\text{ s)} \times (1-\text{PCV})]$$

where area under the curve=the integral of the primary curve and PCV=packed cell volume. Division by (1−PCV) converts plasma flow to blood flow as lithium is distributed only in the plasma fraction of blood. PCV was measured as the value of haematocrit (Kubota Hematocrit KH-120A, Tokyo, Japan) before cardiac output measurement in each haemodynamic state.

STATISTICAL ANALYSIS

The linear regression equations between ThDCO and EMCO, and between LiDCO and EMCO were calculated by simple linear regression analysis using the least squares method. As recommended by Bland and Altman,[17] the difference (ThDCO−EMCO) compared with (ThDCO+EMCO)/2, and the difference (LiDCO−EMCO) compared with (LiDCO+EMCO)/2 were plotted and means (SD) of the differences were calculated. The predictive performance test described by Sheiner and Beal[18] was performed to evaluate statistical significance of the bias (mean prediction error by which ThDCO or LiDCO overestimates or underestimates EMCO) and precision (mean squared prediction error by which ThDCO or LiDCO overestimates or underestimates EMCO) values between two different dilution techniques. One-way analysis of variance followed by the Bonferroni multiple comparison test were used to compare the changes in cardiac output at each haemodynamic state. $P<0.05$ was considered statistically significant, and results are expressed as mean (SD).

Results

The value of EMCO obtained at baseline (1.41 (0.49) litre min^{-1}) was significantly lower than that in the hyperdynamic state (1.74 (0.47) litre min^{-1}), and was significantly higher than that in the hypodynamic state (0.93 (0.43) litre min^{-1}). There was no significant difference between the value of EMCO obtained at baseline (1.41 (0.49) litre min^{-1}) and that obtained at the second baseline (1.36 (0.53) litre min^{-1}). Three aberrant LiDCO readings and 20 ThDCO readings were rejected to obtain 80 readings, respectively. The correlations between ThDCO and EMCO, and between LiDCO and EMCO are shown in figure 1. The correlation

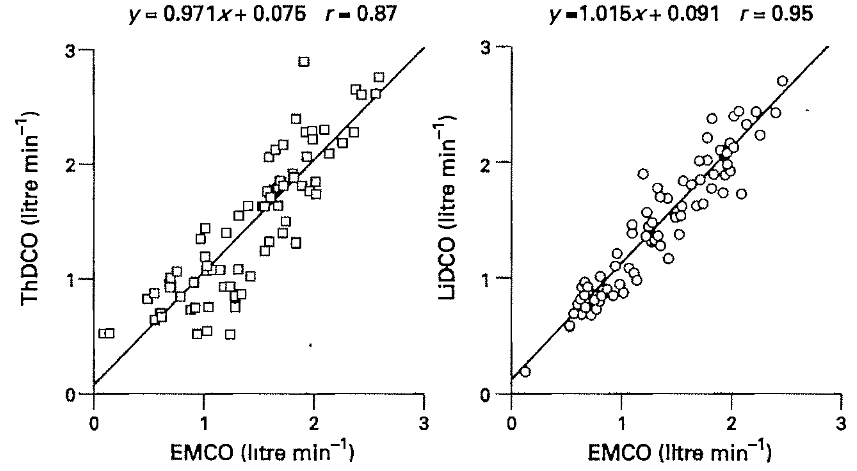

Figure 1 Linear regression between ThDCO and EMCO (left) and between LiDCO and EMCO (right). ThDCO=Thermodilution cardiac output measurement; LiDCO=lithium dilution cardiac output measurement; EMCO=cardiac output measured by electromagnetic flowmetry.

Table 1 Bias and precision values of ThDCO and LiDCO in predicting EMCO in each haemodynamic state (bias, precision). ThDCO=Thermodilution cardiac output measurement; LiDCO=lithium dilution cardiac output measurement; EMCO=cardiac output measured by electromagnetic flowmetry. *$P<0.05$ compared with bias value of ThDCO. †$P<0.05$ compared with precision value of ThDCO

	Baseline 1	Hyperdynamic state	Baseline 2	Hypodynamic state	All data
ThDCO	−0.03, 0.06	0.04, 0.17	0.09, 0.07	0.03, 0.08	0.03, 0.09
LiDCO	0.10*, 0.03	0.01, 0.02†	0.18, 0.06	0.17, 0.06	0.11*, 0.04†

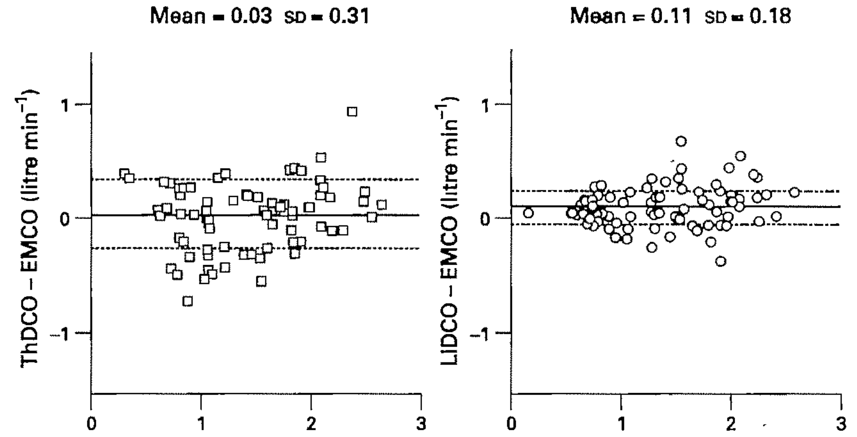

Figure 2 Difference between ThDCO and EMCO plotted against mean (left) and difference between LiDCO and EMCO plotted against mean (right). The thick line shows the mean; broken lines indicate ±1 SD. ThDCO=Thermodilution cardiac output measurement; LiDCO=lithium dilution cardiac output measurement; EMCO=cardiac output measured by electromagnetic flowmetry.

coefficient of the linear regression line between LiDCO and EMCO (0.95) was higher than that between ThDCO and EMCO (0.87).

The bias and precision values of ThDCO and LiDCO in predicting EMCO in each haemodynamic state are given in table 1. The bias values of LiDCO were greater than those of ThDCO, except in the hyperdynamic state, and the precision values of LiDCO were less than those of ThDCO in each state. However, there was no significant difference in bias and precision values between the two methods, except the bias value at baseline 1 and the precision value in the hyperdynamic state. Taking all haemodynamic states together, the precision value of LiDCO (0.04) was significantly less than that of ThDCO (0.09), and the bias value of LiDCO (0.11) was significantly greater than that of ThDCO (0.03) (table 1).

The difference (ThDCO−EMCO) compared with (ThDCO+EMCO)/2, and the difference (LiDCO−EMCO) compared with (LiDCO+EMCO)/2 are shown in figure 2. The SD of the differences (LiDCO−EMCO) (0.18) was less than that of the difference (ThDCO−EMCO) (0.31).

Discussion

The reliability of LiDCO compared with ThDCO was assessed under general anaesthesia by comparing both with EMCO at baseline and during hyperdynamic and hypodynamic states. As we did not measure coronary blood flow, which constitutes approximately 5% of left ventricular output under resting conditions and increases by approximately 15% under hypoxia,[19] ThDCO and LiDCO should exceed the values of EMCO. The bias values of LiDCO and those of ThDCO showed positive values except for ThDCO at baseline 1 (table 1). The bias values of LiDCO were greater than those of ThDCO, except in the hyperdynamic state. The bias value of LiDCO (0.11) calculated for all haemodynamic states was significantly greater than that of ThDCO (0.03). However, bias is affected by coronary blood flow, which was not measured in our study. The precision values of LiDCO calculated for all haemodynamic states, and for each individual haemodynamic state, were significantly less (i.e. better) than those of ThDCO (table 1). These results suggest that the variation in each prediction of cardiac output by LiDCO was lower than that by ThDCO, and the LiDCO technique gave better repeatability than the ThDCO technique. Furthermore, the correlation coefficient of the relationship between LiDCO and EMCO was higher than that between ThDCO and EMCO, and the SD of the differences (LiDCO−EMCO) was less than that of the difference (ThDCO−EMCO). Our results indicate that the LiDCO technique was more reliable than the ThDCO technique.

Although the thermodilution technique with a pulmonary artery catheter has been used widely, bolus injection of ice-cold 5% glucose elicits haemodynamic changes such as slowing of heart rate,[20–22] decrease in systemic arterial pressure,[23] increase in stroke volume[24] and arrhythmias such as atrial fibrillation[25] or ventricular fibrillation.[26] Several researchers have reported severe complications resulting from pulmonary artery catheterization in addition to central venous puncture complications.[1–3] In a recent prospective cohort study, Connors and colleagues analysed 5735 critically ill adult patients receiving care in an intensive care unit.[4] They compared outcome in two groups of patients (matched for severity of illness): one group had pulmonary artery catheters inserted and the other did not. They found that pulmonary artery catheterization was associated with a 24% higher mortality, longer hospital stay and increased medical costs. As the thermodilution technique uses cold as an indicator, several factors may influence cardiac output estimation by this method.[27] Renner, Morton and Sakuma[28] conducted an animal study to determine the accuracy and reproducibility of the thermodilution technique using 5- or 10-ml room temperature or iced injectates. Their results showed that a smaller volume of room temperature injectate impaired accuracy but not reproducibility at low cardiac outputs, and that this same volume impaired reproducibility at high cardiac outputs.[28] Thermodilution measurements obtained at specific times during the respiratory cycle are known to vary by 5–20%.[29–31] Measurement errors caused by even a small cyclical variation in pulmonary blood temperature with respiration may be another factor in the variation of results in thermodilution techniques. Even if the end of expiration is used to time injection of the indicator, cardiac output is underestimated during spontaneous breathing and overestimated during continuous or intermittent positive-pressure ventilation.[32] Variations in pulmonary artery blood temperature transiently increase after cardiopulmonary bypass, and the increased thermal noise may cause significant errors in the results of thermodilution techniques.[33] Wetzel and Latson[34] reported that cardiac output was underestimated during rapid volume infusion because rapid peripheral volume infusion causes small fluctuations in pulmonary artery blood temperature. In our study, ThDCO was performed using 5 ml of ice-cold 5% glucose as the indicator and was measured during apnoea at the end of expiration to reduce baseline fluctuations in pulmonary artery blood temperature.

The lithium dilution technique causes less of a problem from loss of indicator. It cannot be lost through the injection catheter and it is not lost in its passage through the lungs, nor does it bind to plasma or tissue proteins.[13 14] Because we stopped mechanical ventilation and maintained i.v. infusion rates constant while cardiac output was measured, we kept fluctuations in baseline voltage by respiratory cycle or rapid volume infusion to a minimum. Lithium chloride injection did not elicit any haemodynamic changes. As it does not require the use of a pulmonary artery catheter, the lithium dilution technique is a less invasive method; measurements can be taken via *in situ* central venous and arterial catheters without exposing patients to any of the risks associated with the use of a pulmonary artery catheter.

Several caveats with the LiDCO system should be mentioned. (1) We administered heparin 100 u. kg^{-1} to avoid blood clotting on the sensor because clotting would cause rapid deterioration of the electrode. The sensor used in our study was a prototype disposable one, not treated with anticoagulant. We used one sensor throughout each experiment because of limited availability of the prototype sensors and because of this, administration of heparin was essential. (2) Linton, Band and Haire[12] reported that the sudden transition from room temperature saline to warm blood caused a transient drift in electrode potential. We observed this in our study; however, we had enough time for blood sample withdrawal (10–15 s) to stabilize the drift of the lithium sensors before measurement. (3) We observed a transient increase in baseline voltage for a few minutes starting just after administration of $NaHCO_3$, vecuronium or pancuronium. Although these drugs do not cause permanent unacceptable drift or deterioration of the electrode, it should be kept in mind that administration of these drugs during or immediately before the measurement time may decrease the accuracy of the lithium dilution technique. (4) The LiDCO system requires obtaining 4 ml min^{-1} of sample blood; mean blood loss for each measurement was 2.6 ml, which was less than that in the system reported by Linton, Band and Haire[12] (who withdrew 15–30 ml min^{-1}). Because the sensor is located outside the artery, sample volume loss may be unavoidable, but a decrease in sample volume may be realized in the future if a smaller sensor is designed or sample reinfusion is made possible.

The lithium dilution technique requires further examination concerning pharmacokinetics and the future safety of multiple injections of lithium chloride in clinical settings. As lithium has been administered orally as the carbonate salt (Li_2CO_3) in the treatment of many affective disorders to produce therapeutic plasma concentrations (0.5–0.8 mmol litre^{-1} obtained 12 h after the last lithium dose), the side effects and toxicity are well known. Lithium carbonate is usually prescribed in a dose of 600– 1200 mg (corresponding to 33.2–66.4 mmol of lithium ion) daily in divided doses.[35] Linton, Band and Haire,[12] who administered 0.6 mmol of lithium chloride in one measurement, reported that the peak concentration of lithium was 1.3 mmol litre^{-1} only a few seconds after administration, and they found that awake subjects experienced no sensations when given doses of lithium chloride up to 1 mmol i.v. We carried out LiDCO eight times in one experiment with the dose level at 0.1 mmol (0.67 ml of a 0.15-mol litre^{-1} solution). In our study, we did not measure the concentration time course of lithium after experiments, but the mean peak concentration of lithium appearing for a few seconds in dilution curves was 0.89 mmol litre^{-1} (maximum 1.44 mmol litre^{-1}, minimum 0.31 mmol litre^{-1}). Although the amount of lithium administered by the i.v. route in one measurement is much less than that administered by the oral route in the treatment of affective disorders, pharmacokinetics and the emergence of side effects by multiple injections over a short time should be investigated to determine safety and dose limitations.

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Detection of arrhythmogenic cellular magnesium depletion in hip surgery patients

G. ZUCCALÀ, M. PAHOR, F. LATTANZIO, S. VAGNONI, F. RODOLÀ, P. DE SOLE, A. CITTADINI, A. COCCHI AND R. BERNABEI

Summary

The use of high-dose magnesium infusions in critically ill and surgical patients is increasing. This practice is associated with considerable risk of toxicity, as no reliable criteria are currently available to detect significant intracellular magnesium depletion. We have evaluated, before and after surgery, 33 elderly patients with hip fracture, by 24-h Holter ECG monitoring, Doppler echocardiography and serum chemistry; lymphocyte magnesium was measured using atomic absorption spectrophotometry. The severity of ventricular arrhythmias increased, and serum and mononuclear magnesium concentrations decreased significantly after surgery. Decreases in either serum magnesium concentrations >0.125 mmol litre^{-1} or cellular magnesium >6 nmol mg^{-1}, but not serum or lymphocyte absolute magnesium concentrations, were associated with postoperative development of repetitive arrhythmias. Variations in serum magnesium concentrations correlated with intracellular decreases, and yielded good accuracy in predicting the postoperative worsening of arrhythmias. Thus perioperative differences in serum magnesium concentrations reflected intracellular variations and allowed us to identify patients with clinically relevant cellular magnesium depletion. (*Br. J. Anaesth.* 1997; **79**: 776–781).

Key words
Ions, magnesium. Complications, magnesium depletion. Heart, arrhythmia. Measurement techniques, spectrophotometry. Surgery, orthopaedic.

In recent years magnesium depletion has proved a common condition in patients with acute myocardial infarction[1–3] in the intensive care unit and after major surgery.[4–12] Magnesium deficiency has been associated with increased occurrence of cardiac arrhythmias, both after operation[8–12] and in acute myocardial infarction.[13–15] In addition, hypomagnesaemia has been associated with increased mortality both in postoperative and intensive care patients.[16 17] Thus routine magnesium therapy is expected to be used with increasing frequency in intensive care settings and operating rooms,[18 19] also because of increasing evidence of its beneficial effects on postoperative cardiac function and rhythm, muscle strength, vascular tone and central nervous system metabolism.[10 20–22]

In patients with myocardial infarction, systematic administration of magnesium has been shown to decrease the incidence of ventricular fibrillation, but with detrimental effects on survival.[23 24] This outcome was associated with an excess incidence of cardiogenic shock and heart failure;[25] indeed, excessive intracellular magnesium concentrations can depress cardiac function.[26 27] It has been acknowledged that safe and effective magnesium treatment as a clinical routine is still hindered by the lack of correlation between serum and tissue magnesium concentrations; the value of other clinically available methods to detect magnesium deficiency, such as measurement of ultrafilterable magnesium or 24-h urinary excretion, is at best uncertain.[6 9–11 28 29]

Atomic absorption spectrophotometry is the most reliable method currently available to measure intracellular magnesium content.[30] Mononuclear blood cell magnesium concentrations, as determined by this method, correlate well with myocardial concentrations in patients undergoing heart surgery.[11] Nevertheless, this method is too expensive and difficult to implement to be used routinely.[10 11 31]

We have studied a series of older patients undergoing hip surgery to identify any variables that may be useful in clinical practice to detect "relevant" intracellular magnesium depletion, that is independently associated with postoperative development of repetitive ventricular arrhythmias.

Patients and methods

We studied 52 older patients (mean age 80 (range

GIUSEPPE ZUCCALÀ*, MD, FABRIZIA LATTANZIO, MD, ALBERTO COCCHI, MD, ROBERTO BERNABEI, MD (Department of Gerontology); SALVATORE VAGNONI, MD, FERDINANDO RODOLÀ, MD (Department of Anesthesiology); PASQUALE DE SOLE, PHD (Department of Clinical Chemistry); ACHILLE CITTADINI, PHD (Department of Oncology); Catholic University of the Sacred Heart, Rome, Italy. MARCO PAHOR, MD, Department of Preventive Medicine, University of Memphis, TN, USA.
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*Address for correspondence: Department of Internal Medicine and Geriatrics, Catholic University of the Sacred Heart, Lgo F.Vito, 1–00168 Rome, Italy.

Table 1 Perioperative characteristics of the population (mean (SEM) or number (%). SAP=Systolic arterial pressure; DAP=diastolic arterial pressure; LV=left ventricular. *$P<0.05$; ***$P<0.0001$

	Preoperative	Postoperative
Serum albumin (g litre^{-1})	38 (1)	33 (1)*
Serum calcium (mmol litre^{-1})	2.25 (0.02)	2.17 (0.02)*
Serum creatinine (µmol litre^{-1})	83.98 (5.3)	99.9 (19.5)
Serum potassium (mmol litre^{-1})	3.7 (0.5)	3.7 (0.4)
Serum sodium (mmol litre^{-1})	138 (5)	138 (5)
Serum magnesium (mmol litre^{-1})	0.97 (0.02)	0.85 (0.02)***
Cellular magnesium (nmol mg^{-1})	60 (3.6)	54 (3.5)***
SAP (mm Hg)	144 (3.5)	140 (3.5)
DAP (mm Hg)	82 (1)	84 (1)
Diuretic users	10 (30)	
Alcohol (>0.20 oz day^{-1})	2 (6)	
Coffee	4 (12)	
LV mass (g m^{-2})	104 (3.6)	
LV ejection fraction (%)	66 (1)	62 (1)*

61–100) yr) with proximal femur fracture, consecutively admitted to the orthopaedics ward of the University Hospital A. Gemelli from January 1 to June 30, 1994. Patients with pacemaker rhythm (three cases), chronic atrial fibrillation (four cases), pulmonary embolism (three cases), unreliable mononuclear cell magnesium assay (six cases) or those receiving antiarrhythmic drug therapy (three cases) were excluded. Thus the study included 33 subjects (two males, 31 females; mean age 82 (range 62–100) yr) whose characteristics are shown in table 1. Twelve patients suffered from coronary disease, 12 from hypertensive heart disease and four from both conditions; however, no patient showed signs or symptoms, or reported history of heart failure.

SURGERY

Femoral fractures were treated by compression screw-plate in 18 patients and by cemented total hip arthroplasty in 15. All patients received oral diazepam and i.m. atropine as premedication. General anaesthesia comprised induction with thiopentone 3–4 mg kg^{-1} and vecuronium 0.08 mg kg^{-1}, and maintenance with isoflurane and nitrous oxide in oxygen, with fentanyl 4 mg kg^{-1} h^{-1} i.v. During operation, the ECG, non-invasive arterial pressure, pulse oximetry and end-tidal analysis of expired gas were monitored throughout anaesthesia. Postoperative pain was controlled by ketorolac i.v. From the beginning of surgery to the postoperative period, Holter monitoring and blood sample collection, patients received a mean of 5742±772 ml of i.v. fluids, with sodium 598 mmol litre^{-1}, potassium 37.5 mmol litre^{-1}, calcium 3 mmol litre^{-1} and magnesium 6.25 mmol litre^{-1}.

DATA COLLECTION

All patients were evaluated by history, physical examination, blood chemistry, chest x-ray, electrocardiography, Doppler echocardiography and urinalysis. In addition, 24-h Holter monitoring was performed (using a full-disclosure Oxford Medilog RF/12 DR system) 48 h before, and from 18 to 20 h after surgery. Two leads (CM1 and CM5) were recorded and analysed independently by two physicians who were blinded to all clinical data. Ventricular arrhythmias were classified according to Lown and co-workers: class 1 (less than 30 ectopic beats per hour), 2 (30+ ectopic beats per hour), 3 (multifocal beats), 4A (couplets) and 4B (ventricular tachycardia).[32] The fifth class (R-on-T phenomenon) was not recorded in our patients. Doppler echocardiograms were obtained at the beginning of each Holter monitoring; all investigations were performed by a phased-array system, equipped with a 3.5-MHz probe (2.5 MHz during pulsed Doppler sampling). The left ventricular mass was calculated by a validated method.[33]

Mononuclear blood cells were obtained for measurement of intracellular magnesium content within the first hour of each Holter monitoring from duplicate 10-ml samples of heparinized blood, obtained from the antecubital fossa after removing the tourniquet. Lymphocytes were obtained from whole blood by separation on a discontinuous density gradient (Lymphoprep, Nycomed, Oslo).[34] The mononuclear cell layer was washed in isotonic saline and the cell pellet lysed by resuspending in 1.2 ml of distilled water. Immediately after lysis, 0.5-ml aliquots were diluted 1:1 with sodium phosphate buffer 20 mmol litre^{-1}, pH 7.4, for protein analysis, or nitric acid 0.2 mol litre^{-1} for magnesium assay, and stored at −20°C. Protein analysis was carried out using the Bradford method, with 1 mg ml^{-1} of albumin solution as standard.[35] Cell magnesium was measured by atomic absorption spectroscopy.

As it is difficult to measure accurately lymphocyte magnesium concentrations,[31] we obtained duplicate specimens for each patient from a single venepuncture, and these were processed independently. Magnesium mononuclear cell values were used in the study only if the results in the two specimens differed by less than 15% of the mean value of the two specimens.[31] This standard was not met in six (15%) of the duplicate specimens.

STATISTICAL ANALYSIS

Data for continuous variables are presented as mean (SEM). Statistical analysis was performed using EpiInfo III and SPSS for Windows 6.0.1 statistical softwares; differences were considered significant at $P<0.05$. The variations in Lown classification induced by surgery were evaluated by the Wilcoxon matched pairs rank test. Comparisons between pre- and postoperative variables were performed by the two-tailed paired Student's t test. Analysis of variance for normally distributed variables in relation to both postoperative Lown classification and perioperative variations in Lown classes of arrhythmias was performed by ANOVA comparisons; otherwise, non-parametric tests, such as Kruskal–Wallis H, were adopted.

Because no established cut-offs are available to diagnose magnesium depletion, linear discriminant analysis was used to test in separate models the association of perioperative differences in serum and cellular magnesium concentrations with postoperative worsening of ventricular arrhythmias.[36]

Logistic regression analysis with forward stepwise selection of covariates, based on conditional variable estimates, was used to assess the association of cellular and serum magnesium variations with postoperative worsening of Lown classification. As cellular and serum magnesium differences were collinear measures, these variables were analysed in separate models. In the regression models patients with serum and cellular magnesium decreases >0.125 mmol litre^{-1} and >6 nmol mg^{-1}, respectively, were compared with those with lower degrees of magnesium depletion. According to linear discriminant analysis, these thresholds yielded the best accuracy in predicting worsening of ventricular arrhythmias.[36] The following covariates were also examined as potential confounders in the regression models: age; sex; pre- and postoperative serum creatinine, sodium, calcium and potassium concentrations, and their perioperative differences; type and duration of surgery; preoperative Lown classification; amount of fluids and electrolytes administered; occurrence of intraoperative hypotension; occurrence of severe blood loss with necessity of transfusion; presence of cardiovascular disorders; and preoperative cellular and serum magnesium concentrations.

Finally, the Pearson's correlation coefficient for perioperative variations in serum and cellular magnesium was calculated. Also, stepwise linear regression analysis was used to build an equation that predicted the variations in intracellular magnesium from a series of clinically available variables. The covariates entered in this model included: age; sex; presence of cardiovascular disorders; type and duration of surgery; amount of fluids and electrolytes administered; occurrence of intraoperative hypotension; occurrence of severe blood loss with subsequent transfusion; preoperative cellular magnesium concentrations; and the perioperative differences in serum concentrations of magnesium, sodium, calcium, potassium and creatinine.

Results

VENTRICULAR ARRHYTHMIAS

No patient developed significant arrhythmias during surgery. The average frequency of ventricular ectopic beats did not differ between preoperative and postoperative Holter recordings (206 (76) *vs* 214 (102) beat h^{-1}, respectively; P=0.9). However, postoperative worsening of Lown classification of ventricular arrhythmias (table 2) was detected by Holter monitoring in 18 patients (55%), while the severity of arrhythmias was unchanged in 13[37] and decreased in two (6%); the perioperative difference for all patients, as evaluated by the Wilcoxon rank test, was significant (z=2.77, P=0.005). After operation, nine (27%) patients showed repetitive ventricular arrhythmias that were not detectable before surgery. Among these, two (6%) had runs of sustained ventricular tachycardia (from 12 to 30 beats); one died suddenly approximately 24 h after Holter monitoring. There were no signs of pulmonary embolism or myocardial infarction at necropsy, thus supporting the hypothesis of arrhythmic death.

Table 2 Lown classes of ventricular arrhythmias

Class	Preoperative (*n* (%))	Postoperative (*n* (%))
0	8 (25)	6 (18)
1	14 (42)	10 (30)
2	2 (6)	4 (12)
3	4 (12)	2 (6)
4a	5 (15)	9 (28)
4b		2 (6)

BLOOD CHEMISTRY

After surgery, significant reductions in serum albumin, calcium, and in both cellular and serum magnesium concentrations occurred. There were no differences in serum potassium, sodium, chloride, ureic nitrogen, creatinine or phosphate concentrations (table 1).

CORRELATES OF POSTOPERATIVE ARRHYTHMIAS

There were no significant differences in clinical or Doppler echocardiographic variables with respect to postoperative Lown classification of arrhythmias or perioperative variations.

Preoperative Lown classification (P=0.0015) and extent of intracellular magnesium loss (P=0.04) were the only variables associated with postoperative Lown classification. When postoperative worsening of Lown

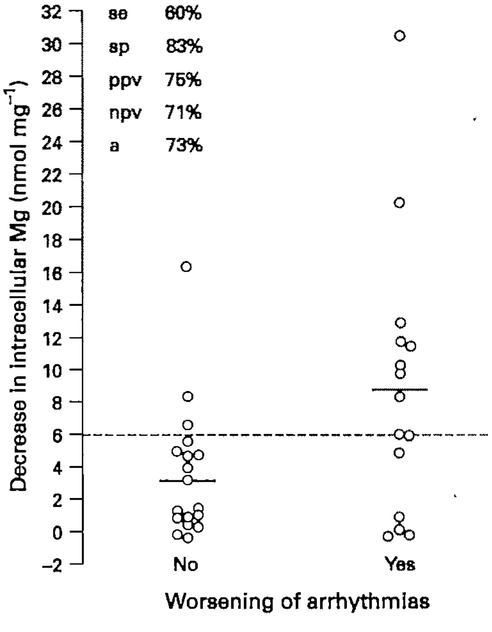

Figure 1 Individual variations in lymphocyte magnesium content according to the postoperative increase in severity of ventricular arrhythmias. The solid lines represent group means; broken line indicates the threshold value (calculated with linear discriminant analysis) above which worsening was most likely to occur. Also shown are sensitivity (se), specificity (sp), positive predictive value (ppv), negative predictive value (npv) and predictive accuracy (a) for this threshold.

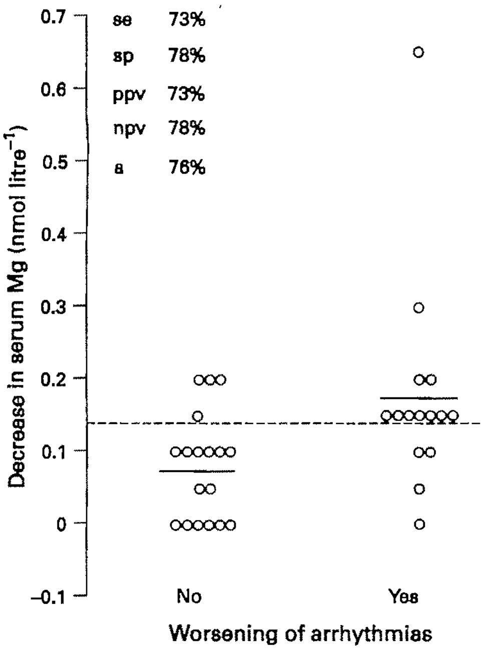

Figure 2 Individual variations in serum magnesium concentrations according to the postoperative increase in severity of ventricular arrhythmias. The solid lines represent group means; broken line indicates the threshold value (calculated with linear discriminant analysis) above which worsening was most likely to occur. Also shown are sensitivity (se), specificity (sp), positive predictive value (ppv), negative predictive value (npv) and predictive accuracy (a) for this threshold.

classification was examined, greater perioperative differences in cellular (P=0.019) and serum (P=0.013) magnesium and in serum calcium concentrations (P=0.005) were the only variables associated with postoperative changes to higher classes.

The linear discriminant analysis indicated that perioperative variations in both cellular (fig. 1) and serum (fig. 2) magnesium concentrations predicted postoperative worsening of ventricular arrhythmias. The best predictive accuracy was obtained using threshold levels of 0.125 mmol litre^{-1} and 6 nmol mg^{-1} as decreases in serum and cellular magnesium, respectively (figs 1, 2).

Perioperative differences in serum and cellular magnesium and in serum calcium concentrations were the only variables that entered the final conditional logistic regression models, and were therefore independently associated with postoperative worsening of arrhythmias. The first two rows in table 3 refer to partial models, not adjusted for difference in serum calcium. It is noteworthy that while the odds ratio for the decrease in serum magnesium was not affected substantially by adjustment for serum calcium difference (model 3), the statistical significance of cellular magnesium depletion was enhanced markedly when serum calcium variation was entered into the model (model 4).

Table 3 Conditional logistic regression results relating the perioperative differences in serum and intracellular magnesium concentrations (evaluated in separate models) to the postoperative increase in Lown classification

	Odds ratio	95% CI	P
Models not adjusted for variations in serum calcium			
Serum magnesium			
(decrease >1.25 mmol litre^{-1})	9.62	1.95–47.4	0.005
Cellular magnesium			
(decrease >6 mmol mg^{-1})	7.50	1.49–37.7	0.014
Models adjusted for variations in serum calcium			
Serum magnesium			
(decrease >1.25 mmol litre^{-1})	8.36	1.37–50.9	0.021
Cellular magnesium			
(decrease >6 mmol mg^{-1})	29.5	2.37–368.3	0.008

CORRELATES OF CELLULAR MAGNESIUM DEPLETION

While pre- and postoperative absolute serum concentrations of magnesium did not correlate with intracellular concentrations, a significant correlation was found between perioperative differences in serum and lymphocyte concentrations (r=0.62; P=0.0001). The perioperative difference in serum magnesium was the only variable that entered the final linear regression model, and was therefore independently associated with variations in intracellular magnesium.

The resulting regression equation was

$$\Delta_{\text{cell}}\ \text{Mg}=1.59+\Delta_{\text{serum}}\ \text{Mg}\times 35.26$$

where Δ_{cell} Mg=perioperative difference in lymphocyte magnesium content (expressed as nmol mg^{-1}), and Δ_{serum} Mg=difference in serum magnesium (mmol litre^{-1}).

Discussion

We have found that postoperative arrhythmogenic cellular magnesium depletion corresponded with a >10% reduction in intracellular concentrations, rather than with a simply "low" total cellular content. In addition, while absolute serum and cellular magnesium concentrations did not correlate, perioperative intracellular variations were associated with differences in serum concentrations by a simple equation, so that patients at risk of development of repetitive ventricular arrhythmias may be identified accurately by monitoring serum magnesium concentrations. Knowledge of variations in intracellular magnesium content from serum assays may be crucial for safe and effective management of high-dose magnesium therapy in patients at risk of magnesium depletion.

Our study focused on detection of postoperative arrhythmogenic cellular magnesium depletion in hip surgery; the clinical value of this study model was confirmed by the significant postoperative increase in repetitive ventricular arrhythmias (table 2). This observation is in agreement with previous observations on the arrhythmogenic role of major surgery; in some studies, magnesium depletion has been identified as the main culprit.[8–12]

In our patients, magnesium depletion was the major determinant of the postoperative increase in severity of arrhythmias (table 3). The independent association of magnesium depletion with postoperative ventricular ectopic activity was significant, even after adjustment for potential confounders, such as potassium and calcium serum concentrations, or their perioperative variations.

The results of this study suggest that postoperative magnesium depletion should be considered in terms of perioperative variations in intracellular concentrations, rather than as "low" total cellular content. This finding is in agreement with experimental studies on magnesium mobilization from cardiac myocytes. These studies showed that most intracellular magnesium is complexed (i.e. inactive) and that only rapid outward magnesium fluxes (ranging from 10 to 15% of total content) yield significant effects on cellular metabolism and electrophysiology through redistribution of subcellular magnesium fractions.[38] Noticeably, the threshold level for the decrease in intracellular magnesium that best predicted postoperative worsening of ventricular arrhythmias in our patients corresponded with approximately 10% of the mean preoperative cellular content (table 1). Other studies also found no relation between total serum or cellular magnesium content and arrhythmias.[29 31 37 39]

Even though simultaneous serum and monocyte magnesium concentrations did not correlate, perioperative differences in serum concentrations reflect intracellular variations, and allow simple prediction of postoperative worsening of ventricular arrhythmias with reasonable accuracy (fig. 2). Indeed, a correlation between changes in serum and myocardial magnesium has been reported in a longitudinal study.[37]

According to the final regression equation, a decrease in serum magnesium concentration of 0.125 mmol litre^{-1} would correspond to a reduction in intracellular concentrations of 5.99 nmol mg^{-1}. These values correspond to threshold levels that in separate models of discriminant analysis best predicted postoperative worsening of arrhythmias (figs 1, 2).

It is unclear why the association between cellular magnesium depletion and worsening arrhythmias was increased after adjusting for serum calcium variations, compared with the unadjusted analysis (table 3). The interrelations between magnesium and calcium variations are complex and not completely understood. Low serum calcium concentrations may enhance cellular magnesium depletion and, conversely, hypocalcaemia can result from magnesium depletion.[10 37 40 41]

In this study, 20 (61%) patients were hypomagnesaemic after surgery; this is similar to the reported prevalence of hypomagnesaemia (69%) after cardiac surgery.[42] The loss of magnesium after surgery has been attributed to intraoperative administration of magnesium-free fluids, and to increased serum cathecholamine concentrations.[7 10 12 29] Similarly, magnesium depletion in patients with acute myocardial infarction has been associated with increased serum noradrenaline concentrations.[13 15] Indeed, massive magnesium release from myocytes has been demonstrated after stimulation with noradrenaline; such an efflux is independent of extracellular magnesium concentrations.[38] In surgical settings, increased noradrenaline serum concentrations have been observed for several days after interventions.[43 44] These observations are in keeping with the reported persistence of magnesium loss during the early postoperative period,[45] and the transient efficacy of single magnesium infusions.[10] Therefore, protracted, high-dose magnesium supplementation has been recommended in patients with acute myocardial infarction or in those undergoing major surgery.[10 18 19 46] However, in large studies in patients with acute myocardial infarction (such as the LIMIT-2 and ISIS-4 studies) treatment with high-dose magnesium has been found either to decrease or increase mortality.[23 46] Sustained monitoring of serum concentrations of magnesium in these patients might allow us to identify subjects with significant intracellular depletion in whom magnesium administration would yield the best risk–benefit ratio.

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British Journal of Anaesthesia 1997; 79: 782–786

Partly exhausted soda lime or soda lime with water added, inhibits the increase in compound A concentration in the circle system during low-flow sevoflurane anaesthesia

G. MORIWAKI, H. BITO AND K. IKEDA

Summary

We performed low-flow sevoflurane anaesthesia at a flow rate of 1 litre min^{-1} in three groups ($n=8$ each) using 600 g of fresh soda lime (control group), 600 g of soda lime with 60 ml of water added (water group) or 600 g of soda lime saturated with carbon dioxide, that is partly exhausted soda lime (carbon dioxide group). Degradation products in the system were measured hourly. Inspired and end-tidal carbon dioxide and sevoflurane concentrations, carbon dioxide and temperature of the soda lime were monitored. $CF_2=C(CF_3)\text{-O-}CH_2F$ (compound A) was the only sevoflurane degradation product detected. The mean maximum concentration of compound A was significantly higher in the control group (mean 16.0 (SD 5.0) ppm) than in the water (1.4 (1.0) ppm) or carbon dioxide (4.0 (1.8) ppm) group, and the maximum temperature of the soda lime was significantly lower in the carbon dioxide group (30.7 (3.5)°C) than in the control (43.4 (1.8)°C) or water (40.8 (1.8)°C) group ($P<0.05$). The use of partly exhausted soda lime or soda lime with water added reduced compound A concentrations in the system during low-flow sevoflurane anaesthesia. (*Br. J. Anaesth.* 1997; **79**: 782–786).

Key words
Anaesthetics volatile, sevoflurane. Equipment, breathing systems. Carbon dioxide, absorption.

Sevoflurane is known to react with carbon dioxide absorbents, resulting in generation of five degradation products.[1 2] Among these degradation products, $CF_2=C(CF_3)\text{-O-}CH_2F$ (compound A) has been reported to be nephrotoxic in rats,[2–5] suggesting that it may be desirable in clinical practice to minimize its production. It has been reported that compound A concentrations in the circle system tend to decrease over time during closed or low-flow sevoflurane anaesthesia[6 7] and that fresh soda lime tends to produce higher concentrations of compound A than partly exhausted soda lime.[8] Therefore, we felt that the use of partly exhausted soda lime (prepared by exposing soda lime to carbon dioxide) rather than fresh soda lime might inhibit the production of degradation products during low-flow sevoflurane anaesthesia. It has also been reported that decreasing the water content of soda lime increases the production of sevoflurane degradation products *in vitro*.[9 10] However, there have been no clinical studies on the effects of soda lime with water added on the generation of degradation products during sevoflurane anaesthesia. In this study, we performed low-flow sevoflurane anaesthesia using fresh soda lime, soda lime with water added and soda lime saturated with carbon dioxide to investigate the effects of these differences in soda lime on the concentration of degradation products in the system.

Patients and methods

This study was approved by the Institutional Committee on Human Research and informed consent was obtained from all patients.

We studied 24 patients, ASA I or II, undergoing tympanoplasty. Patients were allocated randomly to one of three groups ($n=8$ each) to undergo low-flow sevoflurane anaesthesia with three different carbon dioxide absorbents. In the control group, anaesthesia was performed using 600 g of fresh soda lime (Sodasorb II, WR Grace, Lexington, MA, USA). In the water group, anaesthesia was performed using 600 g of fresh soda lime to which 60 ml of distilled water at 25°C was added immediately before use. In the carbon dioxide group, 600 g of partly exhausted soda lime was used. The partly exhausted soda lime was prepared by placing 600 g of fresh soda lime in an anaesthesia system equipped with a 1-litre test lung, with the oxygen flow rate set to 1 litre min^{-1} and a carbon dioxide flow rate of 200 ml min^{-1}, ventilating the test lung with a tidal volume of 500 ml at a rate of 12 cycles min^{-1} for 6 h, and then removing the soda lime and leaving it at room temperature for 6 h.

GOROKU MORIWAKI, MD, HIROMICHI BITO, MD, KAZUYUKI IKEDA, MD, FRCA, Department of Anaesthesiology and Intensive Care, Hamamatsu University School of Medicine, 3600 Handa-cho Hamamatsu 431-31, Japan. Accepted for publication: July 30, 1997.

Patients were premedicated with hydroxyzine 50 mg and atropine 0.5 mg i.m., 30 min before entering the operating room. Anaesthesia was induced with thiopentone 4–5 mg kg^{-1} and vecuronium 0.12–0.15 mg kg^{-1}. After intubation of the trachea and connection to the anaesthesia system, the fresh gas flow rate was set to nitrous oxide 0.6 litre min^{-1} and oxygen 0.4 litre min^{-1}. The lungs were ventilated mechanically with a tidal volume of 10 ml kg^{-1}, and ventilation rate was adjusted to maintain an end-tidal carbon dioxide partial pressure of 4.0–5.3 kPa. The concentration of sevoflurane was adjusted to maintain systolic arterial pressure within ±20% of baseline. The anaesthesia machine used was a Modulas II Anesthesia System (Ohmeda, Madison, WI, USA). The operating room was maintained at a temperature of 25 °C and 50% relative humidity.

The following variables were measured after the start of mechanical ventilation. The temperature of the soda lime was recorded every 15 min using a temperature probe (temperature probe model 9182, Hioki Electric Co., Nagano, Japan) inserted into the centre of the canister. Inspired and end-tidal carbon dioxide concentrations and inspired and end-tidal sevoflurane concentrations were monitored by mass spectrometry (Medical Gas Analyzer 1100, Perkin Elmer, Pomona, CA, USA). Minute carbon dioxide production by the patient was calculated based on minute expired volume and mean expired carbon dioxide concentration. Minute expired volume and mean expired carbon dioxide concentrations were measured using a linearized electric Wright respirometer (BOC Medishield, Essex, UK) and a bypassed mini-mixing chamber for mass spectrometry, respectively. Gas samples for measurement of degradation products were obtained from the inspiratory limb of the anaesthesia system every hour until 3 h after termination of anaesthesia..

Sample gas for measurement of degradation products was collected from the inspiratory limb of the anaesthesia system using a gas-tight syringe (20 ml). Concentrations of degradation products were measured using a gas chromatograph (model GC-9A, Shimadzu, Kyoto, Japan) equipped with a gas sampler (model MGS-5, Shimadzu, Kyoto, Japan). The sample volume was 1 ml. For gas chromatography, the column temperature was 100 °C and the injection inlet temperature was 140 °C; nitrogen was used as the carrier gas at a flow rate of 50 ml min^{-1}. The detector was a hydrogen flame ionization detector (FID). The column was a glass column, 5 m in length, 3 mm internal diameter, filled with 20% DOP Chromosorb WAW (Technolab S.C. Corp., Osaka, Japan), 80/100 mesh. The gas chromatograph was calibrated against a standard calibration gas prepared from stock solutions of compound A.

In order to determine the water content of the soda lime, samples of fresh soda lime were treated in the same way as in each group and the water content was then measured. In addition, three 600-g samples of fresh soda lime and three 600-g samples of fresh soda lime with water added were processed in the same way as the soda lime used in the carbon dioxide group, and the time at which carbon dioxide was no longer absorbed in the inspiratory limb of the circle system was measured.

All values are expressed as mean (SD). The concentration of compound A, temperature of the soda lime, end-tidal sevoflurane concentration and carbon dioxide production were compared by one-way analysis of variance (ANOVA) followed by Bonferroni/Dunn. $P<0.05$ was considered statistically significant.

Results

There were no significant differences in age, height or body weight between the three groups (table 1). The only degradation product of sevoflurane detected was $CF_2=C(CF_3)$-O-CH_2F (compound A). The maximum concentration of compound A was higher in the control group than in the water or carbon dioxide group ($P<0.05$) (table 2). There were no significant differences between the groups in end-tidal sevoflurane concentration at the time of measurement of the individual maximum concentration of compound A (table 2).

The individual maximum temperature of the soda lime was significantly lower in the carbon dioxide group than in the two other groups ($P<0.05$) (table 2). The concentration of compound A in the circle system at each measurement point decreased 60 min after the start of measurement in the following order:

Table 1 Patient characteristics (mean (SD) or range)

	Age (yr)	Height (cm)	Body weight (kg)
Control group	59.3 (36–76)	154.9 (8.5)	53.6 (8.3)
Carbon dioxide group	54.6 (32–68)	155.9 (4 2)	56.0 (8.1)
Water group	59.0 (43–72)	157.4 (7.6)	49.8 (6.5)

Table 2 Maximum compound A concentration, corresponding end-tidal sevoflurane concentration and maximum temperature of soda lime (mean (SD)). Corresponding end-tidal sevoflurane concentration = end-tidal sevoflurane concentration when individual maximum compound A were observed. *$P<0.05$ compared with carbon dioxide group and water group; †$P<0.05$ compared with control group and water group

	Maximum compound A concn (ppm)	Corresponding end-tidal sevoflurane concn (%)	Maximum temperature of soda lime (°C)
Control group	16.0 (5.0)*	1.9 (0.4)	43.4 (1.8)
Carbon dioxide group	4.0 (1.8)	1.7 (0.3)	37 0 (3.5)†
Water group	1.4 (1.0)	1.8 (0.4)	40 8 (1.8)

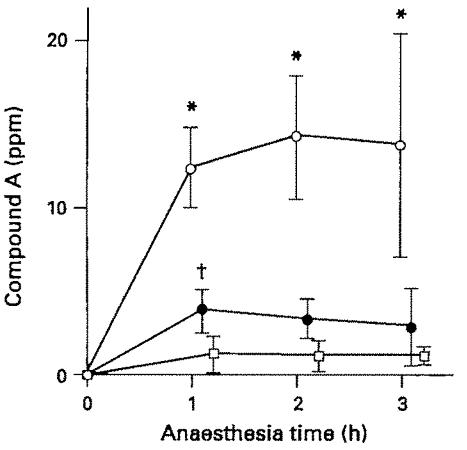

Figure 1 Concentrations of compound A in the anaesthesia system with fresh soda lime (O), partly exhausted soda lime (●) and soda lime with water added (☐) (mean, SD). $^{*}P<0.05$ compared with partly exhausted soda lime and soda lime with water added; $^{\dagger}P<0.05$ compared with soda lime with water added.

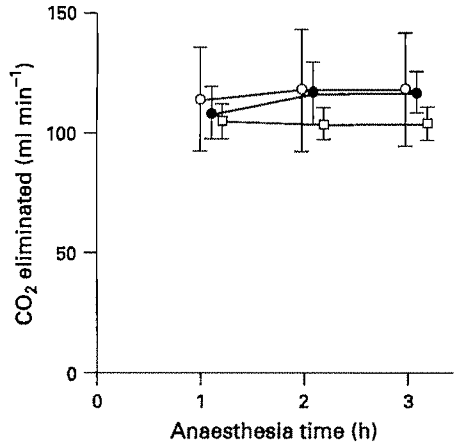

Figure 2 Hourly mean carbon dioxide eliminated by the patient with fresh soda lime (O), partly exhausted soda lime (●) and soda lime with water added (☐) (mean, SD).

control group >carbon dioxide group >water group (i.e. the lowest concentration of compound A was seen in the water group). The differences between the three groups were significant. However, significant differences were observed only between the control and water groups and between the control and carbon dioxide groups at 120 and 180 min ($P<0.05$) (fig. 1).

There were no differences in mean carbon dioxide production per hour between the groups (fig. 2). End-tidal sevoflurane concentrations also did not differ significantly between the groups (fig. 3). In the carbon dioxide group, rebreathing was observed in three of the eight patients, but end-tidal carbon dioxide partial pressure was maintained at 4.0–5.3 kPa until the end of the experiment in these three patients. The water content in the soda lime was 18% in the control group, 8% in the carbon dioxide group and 27% in the water group. Under the conditions used in our study, the soda lime with water added lost its ability to absorb carbon dioxide approximately 1–2 h sooner than fresh soda lime (fig. 4).

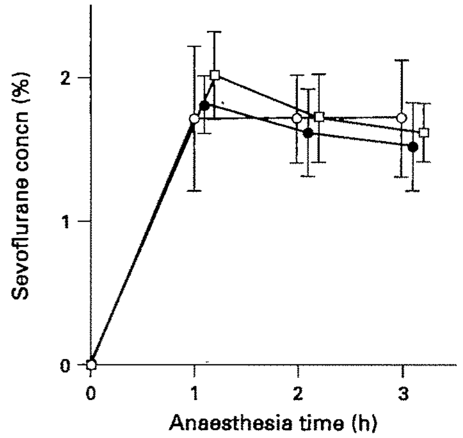

Figure 3 Concentrations of end-tidal sevoflurane with fresh soda lime (O), partly exhausted soda lime (●) and soda lime with water added (☐) (mean, SD).

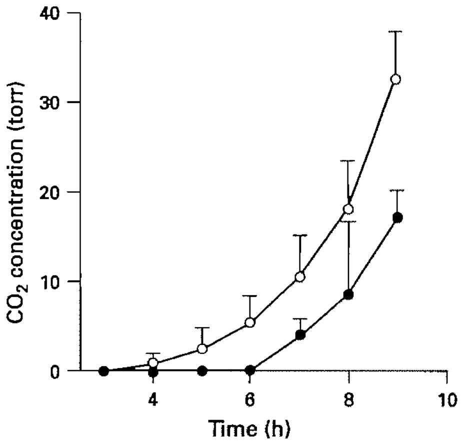

Figure 4 Concentrations of carbon dioxide in the inspiratory limb of the anaesthesia system with fresh soda lime (●) and soda lime with water added (O) (mean, SD).

Discussion

The results of our study indicated that concentrations of compound A in the circle system were reduced significantly during low-flow sevoflurane anaesthesia when partly exhausted soda lime or soda lime with water added, rather than fresh soda lime, was used as the carbon dioxide absorbent. It is unclear if low-flow sevoflurane anaesthesia can lead to renal injury in humans. Some reports indicated that low-flow sevoflurane anaesthesia had no effect on renal function in patients,[11 12] however, at least one study suggested that low-flow sevoflurane anaesthesia could cause renal injury and that compound A in particular might contribute to this injury.[13] It was reported that compound A produced renal injury dose-dependently in rats.[3–5] Therefore, a reduction in compound A concentration in the circle system during low-flow anaesthesia is considered important for ensuring safety.

There are three possible explanations for the successful reduction of compound A in our circle system. The first is that the differences in compound A concentration resulted from differences in the temperature of soda lime. It was found in *in vitro* studies that increasing the temperature of the soda lime increased the degradation of sevoflurane and the production of compound A,[9 14] suggesting that reducing the temperature of soda lime should inhibit the production of compound A in the anaesthesia system.[15] In our study, the mean maximum temperature of the soda lime was 43.4 °C in the control group, and temperatures were 6.4 °C lower in the carbon dioxide group and 2.6 °C lower in the water group, with no significant difference between the water and control groups. Strum, Johnson and Eger[14] showed that the rate of degradation of sevoflurane was related linearly to temperature. However, in our study, the decrease in compound A concentration in the circle system was greater than the decrease in temperature of the soda lime.

The second possible reason for our results is that the differences in compound A concentration resulted from differences in the components of the soda lime. In exhausted soda lime, the components of soda lime (i.e. calcium hydroxide, potassium hydroxide and sodium hydroxide) are reduced by reactivity with carbon dioxide. It has been suggested that the hydroxyl groups present on the components of soda lime might be related to the production of the degradation products of sevoflurane.[16] Therefore, the reactivity of exhausted soda lime with sevoflurane might be reduced because of a decrease in the number of hydroxyl groups, resulting in a decrease in compound A concentration in the circle system.

The third possible reason for our results is that the differences in compound A concentration resulted from differences in water content. The *in vitro* study showed that dry soda lime produces higher levels of sevoflurane degradation products than fresh soda lime,[10] whereas the half-life of sevoflurane in Baralyme increases with increases in added water.[17] Strum and Eger[10] reported that the water content of soda lime decreased from 15% with fresh to 4–8.5 % during routine clinical use. The water content measured in our sample of fresh or partly exhausted soda lime was similar to these values. Thus it can be said that compared with fresh soda lime, partly exhausted soda lime is drier and soda lime with water added is wetter. Considering water content by itself, our results suggested that water tended to increase the production of degradation products in the carbon dioxide group, while it tended to reduce such production in the water group. In our study, the production of compound A at 60 min after the start of measurement was greater in the carbon dioxide group than in the water group, despite the lower maximum temperature of soda lime and differences in the components of soda lime. Although this difference was not statistically significant, the same trend was noted at later times. This may have been a result of differences in the water content of the soda lime in each group.

Considering other factors that are thought to affect the generation of degradation products of sevoflurane, fresh gas flow rate and type of carbon dioxide absorbent (soda lime) were the same in the three groups, and carbon dioxide production by the patient and concentration of sevoflurane in the circle system did not differ significantly between the groups. Thus we concluded that these three contributing factors were interdependent, leading to a decrease in compound A concentration in the circle system in the carbon dioxide group and in the water group. The relative importance of these factors should be assessed in future studies.

Partly exhausted soda lime has a lower carbon dioxide absorbing capacity than fresh soda lime, and therefore the long-term use of exhausted soda lime in anaesthesia may be questioned. In our study, rebreathing was observed in three patients in the carbon dioxide group. This raises the question of the carbon dioxide absorption capacity of soda lime with water added. Our findings indicate that soda lime with water added loses its ability to absorb carbon dioxide only 1–2 h sooner than fresh soda lime, suggesting that it can be used for a period of time.

The results of our study indicated that the use of partly exhausted soda lime or soda lime with water added reduced compound A concentrations in the circle system during low-flow sevoflurane anaesthesia. In particular, soda lime with water added, although its ability to absorb carbon dioxide is decreased, reduced compound A concentrations in the circle system by a factor of 4 compared with fresh soda lime, suggesting that it may prove useful in clinical practice.

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REVIEW ARTICLE

Opioid systems and the newborn

D. F. MARSH, D. J. HATCH AND M. FITZGERALD

The neonatal central nervous system (CNS) is both structurally and functionally immature, and significant changes in opioid analgesic mechanisms occur both before and after birth. Recent research has shown that neonatal pain pathways are different from those of older children and adults, and it is thought that analgesic mechanisms are therefore also likely to differ significantly.[18] However, our understanding of the neurobiology and development of pain pathways is still limited.

In this review we discuss our current understanding of the developmental neurobiology of opioids and the action of opioids in the human neonate. We review briefly background studies of opioid actions in adults and then focus on actions in neonates. The discussion includes both basic laboratory studies and clinical pharmacology, issues which are usually considered separately in the literature. However, if we are to advance our knowledge and improve our management of neonatal pain it is important that they are discussed in relation to one another.

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Key words
Analgesics opioid. Neonates. Model, rat.

Background

While Stertürner isolated morphine, the active ingredient of opium, in 1806, naming it after Morpheus, the God of Dreams, it was not until 1973 that opioid receptors were first described,[58 69 77] shortly before the identification of endogenous opioid peptides.[33] Despite its side effects, morphine is still used widely in the treatment of acute and chronic pain and our knowledge of opioid systems in adults has been the subject of several detailed recent reviews.[15 37 56] Current thinking on adult opioid mechanisms is therefore only briefly summarized.

Opioids act by binding with high affinity membrane receptors which comprise three major groups (mu, delta and kappa receptors) and each receptor can produce different effects. Further division into subtypes remains controversial although there is now evidence of differential effects of delta receptors in mice.[36] We still have little knowledge of the specific function of each receptor, but the recent isolation and cloning of all three will significantly advance research into their roles,[65 78] hopefully assisting the search for clinically useful opioids with highly specific functions and minimal side effects. The endogenous ligands for the opioid receptors are the opioid peptides which can be classified into three groups: enkephalins, endorphins and dynorphins. These endogenous opioids have some agonist activity at all three receptors but each receptor possesses distinct ligand selectivity.[41]

Opioid effects are mediated by several mechanisms in all areas of the CNS, with the predominant effect of decreasing neuronal firing. By stimulation of opioid receptors situated presynaptically on the terminals of neurones, opioids reduce the release of excitatory neurotransmitters involved in pain pathways.[32] Stimulation of postsynaptic receptors inhibits neurotransmission by producing hyperpolarization thus reducing evoked activity.[47] A third possible mechanism involves inhibition of one neurone which lifts inhibition on the second, allowing it to become active in its own inhibitory capacity.[15]

The spinal cord is a very important site of action of opioids where they act to modulate pain pathways. This is evident clinically in the profound analgesia produced by administration of opioids in the extradural and subarachnoid spaces. Afferent nociceptor Aδ and C fibres synapse in laminae 1 and 2 (the substantia gelatinosa) of the dorsal horn[8] and it is here that the majority of spinal cord opioid receptors are located, although a smaller percentage are found in the deeper layers of the dorsal horn.[15] In the rat, mu receptors predominate in the spinal cord, with delta and kappa receptors comprising less than one-third of the total. More than 50% of these opioid receptors are located presynaptically.[7]

The recent proliferation of research into adult pain mechanisms has demonstrated that pain transmission in the spinal cord is not through a simple circuit, but rather the arrival of noxious stimuli from the periphery via primary afferent fibres initiates a cascade of events in the dorsal horn and the complexity of these reactions allows enhancement or modulation of the pain signal.

D. F. MARSH, MB BS, DCH, FRCA, Portex Department of Anaesthesia, Institute of Child Health, Guilford Street, London WC1N 1EH and Department of Anatomy and Developmental Biology, University College London, Gower Street, London WCIE 6BT. D. J. HATCH, MB BS, FRCA, Portex Department of Anaesthesia, Institute of Child Health, Guilford Street, London WC1N 1EH. M. FITZGERALD, BA, PHD, Department of Anatomy and Developmental Biology, University College London, Gower Street, London WCIE 6BT.

Neurotransmitters are released from afferent fibres, interneurones, projection and descending neurones and there is considerable interaction between these fibres. The effects of excitatory amino acids, such as glutamate in particular, have sparked considerable recent interest. Glutamate is abundant in the spinal cord and is released from both myelinated and unmyelinated fibres. Its effects are mediated by NMDA (*N*-methyl-D-aspartate) receptors in addition to non-NMDA receptors, and the former have been shown to play an important role in persistent pain states such as hyperalgesia and allodynia.[84] The NMDA receptor requires repeated or sustained stimulation by C fibres for its activation, and release of glutamate from these fibres stimulates the receptor and initiates a series of intracellular events, resulting in the phosphorylation of intracellular proteins and the opening of an ion channel normally blocked by magnesium. The resultant increase in intracellular calcium allows a greatly augmented response of the receptor to glutamate; this is essentially an elaborate positive feedback mechanism. The activated NMDA receptor leads to many forms of central hyperalgesia.[14] There is now growing evidence that NMDA receptors are involved in the mechanism of opioid tolerance.[51] Mu receptor stimulation by exogenous opioids seems to lead to the same intracellular events which result in "wind-up" of the NMDA receptor and these same mechanisms may also uncouple G-proteins from the mu receptor. This in turn results both in a decreased response of the mu receptor to opioids and activation of the NMDA receptor.[5 51] It is now becoming apparent that opioid receptors do not function in isolation but rely in part on other receptors such as NMDA to elicit their effects.

Supraspinal opioid systems contribute to analgesia by several mechanisms, including decreasing nociceptive input to the brain by altering descending and ascending control systems thereby reducing central perception of pain. Intraventricular injection of opioids in humans is clinically effective in systemically inactive doses, providing evidence for the role of supraspinal sites in the production of analgesia.[44] Intracerebral microinjection of opioid agonists in several species has allowed localization of supraspinal receptors and their contribution to analgesia to be investigated.[85] In rats, opioid receptors are distributed widely throughout the CNS, most densely in the brainstem, thalamus, amygdala, hippocampus and cortex. Mu receptors are found in the majority of these areas, whereas delta receptors are more restricted, found mostly in forebrain regions with poor binding in the midbrain and brainstem. Kappa receptors are distributed widely throughout the forebrain, midbrain and brainstem, comprising only 10% of the total number of receptors in the rat brain but up to one-third in humans.[50] The periaqueductal grey matter and medulla are involved in the descending inhibitory control of dorsal horn neurones. Several supraspinal sites of receptors are found close to the origin of these descending controls, and microinjection of opioids into these areas produces analgesia by their stimulation.

Opioids also act outside the CNS and possess "local analgesic" effects. Laboratory rat studies have demonstrated the peripheral antinociceptive actions of opioid agonists in inflammatory pain models.[73] It is thought that inflammation initiates the axonal transport of opioid receptors to the periphery and increases their number on peripheral nerve terminals; inflammation disrupts the perineurium exposing neuronal opioid receptors.[72] Endogenous peptides are produced by immune cells infiltrating the inflamed tissue.[71] Although clinical evidence is inconclusive, the results of studies of intra-articular morphine for postoperative knee pain are encouraging.[12 31] The local action of a topically applied, systemically inactive opioid lacking central side effects should have major benefits.

Developmental neurobiology of opioid systems

A lack of data in humans has led to increasing reliance on basic studies of laboratory animals in the understanding of the development and function of opioid systems in the human neonate, and the rat has become the acceptable model. The sequence of events that take place in the neurological development of the rat and human CNS are similar but it is difficult to make exact comparisons. Generally speaking, the newborn rat CNS is approximately equivalent to a 24-week human fetus at birth, a full-term neonate at 7 days and a toddler at 3 weeks. Rat CNS maturation is extremely accelerated compared with the human and is mature by 3–4 weeks.[19]

ONTOGENY OF OPIOID RECEPTORS AND LIGANDS

Opioid receptors and endogenous opioid peptides appear very early in CNS development and their ontogeny is non-uniform in the neonatal rat. The majority of receptors in the adult are mu and delta, but early in the postnatal period, on postnatal day 6 (P6), mu and kappa receptors predominate.[45] At birth, opioid receptors are present in several areas, notably the neostriatum, olfactory tubercle, rostral midbrain and later in other areas such as the thalamus and hypothalamus. Delta receptors, however, have a very different ontogeny to mu and kappa receptors and are present in low densities in the brain at birth, progressing to maximum binding in the third postnatal week. A similar pattern of ontogenesis occurs in the spinal cord with the early appearance of mu and kappa receptors and delay in the development of delta receptors until the initial postnatal period.[3]

The pattern of development of mu receptors has been elegantly demonstrated in the rat by *in vitro* quantitative receptor autoradiography. Mu receptor binding sites are concentrated in the superficial laminae of the dorsal horn in the adult, but in contrast at P1, both the superficial and deeper laminae have relatively high densities. The density of mu opioid binding sites peaks at P4, then declines gradually to reach adult levels by the third postnatal week.[38] The change in distribution of mu opioid

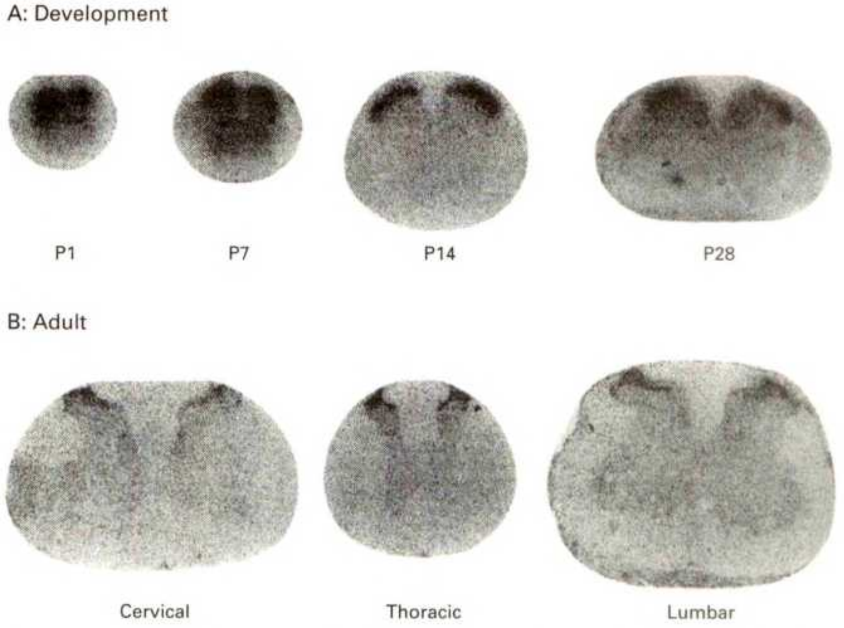

Figure 1 Photomicrographs illustrating μ receptor binding site distribution at P1, P7, P14 and P28 and at different levels of the adult rat spinal cord (modified from Kar and Quirion[38]).

binding sites in neonatal and adult rat spinal cord is shown in figure 1.

Endogenous opioids appear in the mouse brain before opioid receptors on embryonic day 11.5 (E11.5),[67] and enkephalin-like immunoreactivity is detected in rat brain at E18.[59] In human fetal spinal cord, enkephalin-like immunoreactive fibres have been detected as early as 10 weeks.[10] At E16, endorphin concentrations are much greater than enkephalin concentrations with highest concentrations in the phylogenetically newer areas of the brain such as the diencephalon and telencephalon, with a rich distribution in the limbic system. These two peptide systems appear to develop differently, with a marked increase in enkephalin concentrations during the initial perinatal period. Between P6 and P25, both endorphin and enkephalin concentrations increase to approximately adult levels.[6]

DEVELOPMENT OF SPINAL PAIN PATHWAYS RELATED TO OPIOID FUNCTION

As described, opioids play a role in pain transmission in adults by initiating descending inhibitory controls from the brainstem to the spinal cord, and by reducing the resultant activity primarily of C fibres but also of Aδ fibres in the substantia gelatinosa.

In the neonatal rat, considerable development of these pathways occurs postnatally. Although anatomically intact at birth, there is no functional descending inhibitory control until P10–12, reaching adult levels only at P22–24. This is possibly because of a delay in the development of interneurones and because of low concentrations of neurotransmitters in the postnatal period,[21] and presumably underlies the lack of brainstem stimulus-produced analgesia in newborn rats until P21.[79] C fibre and small diameter A fibres grow into the spinal cord a few days before birth, C fibres developing a considerable number of connections in the early postnatal period. However, C fibres are unable to evoke spike activity in the dorsal horn until the second postnatal week. A-fibre terminals are more widespread in the newborn terminating superficially in lamina 2 in addition to deeper laminae.[20] There is evidence that A fibre input is enhanced during this time.[34,35]

In the substantia gelatinosa of the neonatal rat, NMDA induced increases in intracellular calcium are increased markedly, gradually decreasing to adult levels. C fibre induced, NMDA mediated effects in the adult such as wind-up and central sensitization are probably more marked in the neonate, and may contribute to the establishment of C fibre connections in the cord. As in the adult, opioid receptors possibly have close links with the NMDA receptor, and their function in this respect is still unknown.[17]

ANALGESIC ACTIONS

There is ample evidence that these endogenous opioid systems contribute to functioning analgesic mechanisms in the early postnatal period, although the pattern of development of effects is difficult to establish as nociceptive physiology itself changes markedly with age, and a comparable nociceptive stimulus at different ages may be impossible to achieve. Exogenous opioids and their analgesic efficacy have been investigated in the developing rat, but difficulties in behavioural testing of neonatal animals may in part explain apparent discrepancies in the results. Preliminary data from our own laboratory have shown major difficulties with thermal testing of neonatal rats, as limb withdrawal tests seem to rely on many variables. However, despite these problems in methodology, the effect of morphine was shown to increase with age in neonatal rat pups, progressing to a 40-fold analgesic potency at P14 compared with P3 when demonstrated by a limb withdrawal test of thermal analgesia.[22] Similar results were obtained in another study of morphine analgesia in developing rats in which it was shown that morphine had no detectable effect on a tail-flick nociceptive test until P12, reaching analgesic potency comparable with adult levels at P14.[4] Comparing morphine, a potent mu agonist, and ketocyclazocine, a kappa agonist, in the developing rat revealed that morphine was more potent than ketocyclazocine in producing analgesia to limb withdrawal tests of thermal nociception, exhibiting analgesia in a dose dependant manner as early as 3 days in starting doses of 1–2 mg kg^{-1}, with peak effects at 14 days. Ketocyclazocine was more effective at producing analgesia to a mechanical stimulus (a blunt probe applied with a force of 10–15 g) in younger animals, with onset of effect at 7–10 days, this differential development in analgesic patterns confirming a non-uniform ontogeny of opioid receptors.[4] However, unlike thermal and mechanical tests of pain, the response of neonatal rats to the tonic nociceptive effects using the formalin test revealed a similar response to that seen in adults at P3. In this study it was revealed that this response was attenuated by morphine in a dose of 1–2 mg kg^{-1}, in a manner similar to adults.[55]

Early studies have warned of the susceptibility of neonates to the CNS depressant effects of opioids, but a comparison of the sedative and analgesic effects of systemic morphine and pentobarbitone in infant rats ranging in age from 1 to 20 days showed that morphine 1 mg kg^{-1} produced analgesia to an intra-plantar injection of formalin at all ages, which was different qualitatively from the sedative effects of pentobarbitone 10 mg kg^{-1}.[1] Early studies indicated that neonates were more susceptible to the convulsant effects of morphine but an investigation of the effects of high-dose morphine on EEG recordings and behavioural observations showed that although all doses of morphine used produced electrographic spikes in 1-, 3- and 6-day-old neonatal rats, behavioural convulsions were not observed suggesting morphine is less toxic than originally thought.[80]

ACTIONS OF OPIOIDS AT A CELLULAR LEVEL

There is now ample evidence to show that opioid systems play a significant part in the regulation of neuronal development in the neonate. The role of endogenous opioids in neural plasticity has been demonstrated by examining the effects of continuous receptor block on the developing neurones in the cerebral cortex, hippocampus and cerebellum in 10-day-old rats. Neonatal rats were given daily injections of the potent opioid antagonist naltrexone from P0, and after sacrifice on P10 it was demonstrated that the lengths of oblique dendrites of pyramidal cells in the cerebral cortex and basilar dendrites of the hippocampus were significantly increased compared with the control group. The dendritic lengths of spiny branches of cerebellar Purkinje cells were also increased. Endogenous opioids can therefore exert a marked influence on dendritic elaboration and spine formation.[29] In a similar study the effect of exogenous opioid block was examined at P10 and P21. Daily injections of naltrexone were given in a dose of 50 mg kg^{-1} providing complete continuous block, with 1 mg kg^{-1} producing only intermittent opioid receptor antagonism. Continuous block produced large increases in dendrite and spine elaboration at P10, but these increases were only seen in the hippocampus at P21. With intermittent block, dendrite and spine growth were often subnormal.[30] The action of met-enkephalin on the growth of astrocytes in *in vitro* mixed glial cultures were studied in 1-day-old mouse cerebral hemisphere. Continuous treatment with either met-enkephalin, a met-enkephalin–naloxone combination or naloxone alone revealed that met-enkephalin caused a decrease in total cell numbers compared with naloxone-treated cultures and controls. These results suggest that the endogenous opioid met-enkephalin suppresses astrocyte growth by a receptor-mediated mechanism.[74]

These results indicate that endogenous opioids act as inhibitory growth factors in neuronal development, probably by inhibition of DNA synthesis. After a single dose of either met-enkephalin or naloxone to 11-day-old rats, DNA synthesis was shown to be increased in the naloxone-treated group but decreased in the met-enkephalin group.[81] Comparing the effects of morphine on DNA synthesis in neonatal rat brain *in vivo* and *in vitro*, it has been shown that morphine inhibits DNA synthesis *in vivo* in animals aged 1–4 days but not in older animals. The *in vivo* effects were blocked by pretreatment with naloxone indicating a receptor-mediated mechanism. Naloxone administered acutely or naltrexone chronically had no effect. Brain tissue incubated with morphine *in vitro*, however, showed no difference in DNA synthesis compared with controls, indicating an indirect mechanism in the control of cell proliferation.[40]

Reduced latencies to tail-flick tests have been demonstrated on day 9 in neonatal rat pups from P1 to P7 when β-endorphin (in doses of 1–50 μg per pup) was administered daily, suggesting hyperalgesia. In these animals, the number of opioid receptors in the brain was reduced when examined on P14.[86] Studies on neonatal rat pups exposed to morphine either *in utero* (pregnant rats given an s.c. morphine pellet on E16) or postnatally (daily injections of morphine 5 mg kg^{-1}) have demonstrated that chronic morphine exposure results in a significant decrease in brain mu receptor density until day 8, gradually increasing to control levels by day 14. These changes were accompanied by tolerance to the analgesic action of morphine, although there was no significant change in delta and kappa receptor densities.[76] An autoradiographic study of neonatal rat brain compared the neuroanatomical pattern of opioid receptor changes in controls and animals treated chronically with morphine. In those receiving morphine from P1 to P4, mu receptor density on P5 was non-existent in parts of the striatum and decreased in other areas such as the amygdala. Longer treatment with morphine from P1 until P8 produced no additional alterations in mu receptor density.[75]

Little is known of the long-term effects of opioid administration in the neonatal period on the developing CNS in humans.

IMPLICATIONS OF BASIC STUDIES

The results from animal experiments suggest that opioid actions differ with age in the neonate, but the early literature is confused, and more studies are required in this area. Prolonged exposure of the newborn rat to morphine has been shown to have an effect on neuronal development and alterations in receptor expression demonstrate the marked plasticity of opioid systems in the rat neonate. However, pain itself in the neonatal period may also adversely affect this development. With the recent increase in the use of opioids in human neonates,[13 62] there is clearly a need to increase our understanding of the development of opioid systems and the factors modulating this development.

Neonatal opioid pharmacology

The pharmacology of opioids in the newborn has been reviewed recently in an excellent article by Hartley and Levene.[28] This article, therefore, examines the current knowledge of the effects of opioid administration in human neonates.

Morphine and semi-synthetic opioids

Morphine, and its semi-synthetic derivatives codeine and diamorphine, rely in part on the production of metabolites for activity. Because of the large variation in pharmacokinetics of these drugs in neonates, metabolite production can be unpredictable.[28] A recent emergence of more sensitive and specific measurements of metabolites using high pressure liquid chromatography has allowed more detailed investigation of the pharmacokinetics of opioids in neonates, but the difficulties in assessing pain in these pre-verbal patients has left us with little knowledge of the analgesic efficacy of the parent drugs and perhaps, more importantly, their metabolites.

MORPHINE

Morphine is a naturally occurring alkaloid derived from the unripe seed pod of the opium poppy.[9] Among paediatric anaesthetists, it is the most commonly used opioid both during and after surgery.[13]

Morphine is metabolized predominantly in the liver to morphine-3-glucuronide (M3G) and morphine-6-glucuronide (M6G).[9] Glucuronidation is facilitated by uridine diphosphate glucuronosyltransferases (UDPGT), a family of isoenzymes of which 11 different forms have been identified.[49] Both M3G and M6G have significant pharmacological properties.[24] M6G is a potent analgesic and respiratory depressant both in humans and in experimental animals,[25 57] but M3G, the predominant metabolite, is thought to be antagonistic to the analgesic effects of morphine and M6G.[70]

The effects of morphine are therefore dependent on the ratio of M6G:M3G produced,[43] and differential maturation of UDPGT enzymes in the premature and term neonate may produce an evolving ratio of M6G:M3G after morphine administration. This may in part explain a large variation in the effects of morphine in neonates. In premature neonates, the M6G:M3G ratio is related inversely to birth weight, and decreases significantly with increasing birth weight and gestational age.[27]

What is the analgesic efficacy of morphine in the neonate? Most research has concentrated on the adequacy of sedation of neonates undergoing ventilation in the intensive care unit. In one such study, comfort scores incorporating both behavioural and physiological variables were used to assess the adequacy of sedation in premature and term neonates requiring continuous morphine infusions during mechanical ventilation for respiratory distress syndrome. There was no significant difference in the correlation between plasma morphine and analgesic effect in these two age groups. Adequate sedation occurred in 50% of patients with a plasma morphine concentration of 125 ng ml^{-1} (95% confidence interval 116–135 ng ml^{-1}).[11] Studies of the analgesic effects of morphine and its metabolites in post-surgical, spontaneously breathing neonates are urgently required before we can adopt a more informed approach to the use of this opioid.

Kupferberg and Way, in 1960,[42] deduced that the increased sensitivity of neonatal rats to morphine was caused by the greater permeability of the blood–brain barrier. A study by Way, Costley and Way in 1965[83] compared carbon dioxide response curves after morphine and pethidine in eight spontaneously breathing neonates before surgery. The authors found that with morphine 0.05 mg kg^{-1} the carbon dioxide response curve shifted to the right to a greater degree than with pethidine 0.5 mg kg^{-1}. The doses were chosen on the assumption that they were equi-analgesic, and no consideration was given to the consequences of maternal pethidine administration (some had pethidine before delivery) in the immediate postnatal period. Although they concluded that morphine was a more powerful respiratory depressant than pethidine, the statistical and clinical significance of these results was not discussed. Early studies such as these have probably done much to enhance the perception that opioids, in particular morphine, are potent respiratory depressants in the neonate and should only be used with extreme caution.

Subsequent studies, however, do not necessarily agree. A retrospective study of the use of opioids in neonates found that 13% of spontaneously breathing neonates developed apnoea or respiratory depression, thought to be caused by opioids.[61] Nineteen percent of these babies received morphine but none developed respiratory complications, all of which were attributable to papaveretum or pethidine. In comparing the respiratory effects of morphine infusions in neonates and children after cardiac surgery, no age-related differences were found, and it was concluded that neonates have the same ventilatory response to morphine as infants and children at the same plasma concentration.[48]

We now have much more knowledge of morphine pharmacokinetics and the activity of its metabolites, and it is possible that if equi-analgesic rather than "scaled-down" adult doses are given, the risk of serious respiratory depression would be no greater.

Studies of morphine use in neonates have not reported any significant cardiovascular side effects such as bradycardia or hypotension.[26 39]

CODEINE

Codeine, or methylmorphine, is a semi-synthetic opioid produced by the substitution of a methyl group for the hydroxy group on carbon 3 of morphine. Ten percent of codeine is demethylated in the liver to form morphine, which is likely to be the main contributor to its analgesic effects.[63] The remainder is demethylated to the inactive norcodeine which is either conjugated or excreted unchanged in urine.

Despite a marked increase in its use among paediatric anaesthetists since 1988,[13 64] data on its kinetics are lacking and we have minimal information on the pharmacodynamics of codeine in neonates. Case reports of adverse reactions such as vasodilatation, severe hypotension and apnoea in infants and children after i.v. administration have precluded its use by this route in all age groups.[68] In the retrospective study of opioid use discussed above, respiratory depression and apnoea occurred in two of 26 spontaneously breathing babies who received i.m. codeine phosphate 1 mg kg^{-1} after operation, although the number of doses was not recorded.[61]

Although there are no data available for neonates, it is likely that immature hepatic metabolic pathways may cause prolonged half-lives of both codeine and subsequently morphine, resulting in an unpredictable quality of analgesia. More research is required if we are to use this opioid effectively.

DIAMORPHINE

Diamorphine is used less commonly than morphine as a sedative for neonates in the intensive care unit, and it is rarely used for postoperative analgesia. Diamorphine is a semi-synthetic opioid produced by the acetylation of morphine. In adults it is deacetylated rapidly in plasma after systemic administration to 6-monoacetyl morphine (6-MAM) by the action of the enzyme plasma cholinesterase, with a half-life of approximately 3 min.[46] 6-MAM is relatively fat soluble and enters the CNS readily where it is probably further de-acetylated to morphine. It is thought that these two active metabolites contribute greatly to the analgesic effect of diamorphine, which is considered to act as a pro-drug.[82]

The effects of diamorphine were studied in 34 premature neonates (gestational age 26–40 weeks) requiring sedation for mechanical ventilation, after a loading dose of 50 $\mu g\ kg^{-1}$ followed by an infusion of 15 $\mu g\ kg^{-1}\ h^{-1}$. A transient decrease in mean arterial pressure was noted at 30 min, coinciding with a statistically significant decrease in heart rate. These effects were not considered clinically significant. However, a significant decrease in ventilatory frequency at 30–60 min was felt to be beneficial in allowing synchrony with the ventilator. This dose regimen provided a mean steady state morphine concentration of 62.6 ± 20.8 ng ml^{-1} and resulted in adequate sedation in all neonates.[16] It was concluded that diamorphine can provide safe sedation for premature neonates undergoing ventilation in the intensive care unit.

Synthetic opioids

Fentanyl, alfentanil and sufentanil are synthetic opioids derived from pethidine. The parent compounds are potent analgesics and their metabolites are either weak analgesics or inactive.[54] As they do not rely on metabolism for activity, they would seem to be a more logical choice of opioid to treat neonatal pain. However, their pharmacokinetics are still very variable in this age group.[28] A low therapeutic index and fears of respiratory depression have precluded their use as postoperative analgesics in spontaneously breathing neonates but they are commonly used during anaesthesia and as sedatives for patients requiring intensive care.

FENTANYL

Fentanyl is a synthetic opioid agonist derived from the phenylpiperidines with an analgesic potency 50–100 times that of morphine. This may be explained by its high lipid solubility and therefore ease of access to the CNS, and after i.v. injection it is distributed widely to the tissues and viscera. In the adult, metabolism is hepatic with less than 6% of the unchanged drug excreted in urine. This is primarily by de-alkylation to norfentanyl but also by hydroxylation of fentanyl and norfentanyl by the isoenzyme system cytochrome P450.[54] A short duration of action and more predictable pharmacokinetics are reasons for its popularity as an analgesic during major surgery and as a sedative in the intensive care unit. A narrow therapeutic index and side effects such as respiratory depression have hampered its use as a postoperative analgesic, both in adults and children.

In order to determine a dose regimen for fentanyl use in neonates undergoing ventilation for respiratory distress syndrome, its effects were compared in 20 newborn and premature neonates with a control group who did not receive fentanyl. The mean dose required to produce adequate sedation was 0.64 $\mu g\ kg^{-1}$ in neonates of less than 34 weeks gestational age, increasing to a mean of 0.75 $\mu g\ kg^{-1}$ in those 34 weeks or older. Mechanical ventilation was tolerated well in the fentanyl group compared with controls, without the need for additional sedation or analgesia. There were no significant cardiovascular side effects in the fentanyl group and no reports of rigidity of the thorax.[66] Interestingly, a significant change in the pharmacodynamic response with time was found in eight neonates requiring sedation during extracorporeal membrane oxygenation for respiratory failure in the first few days of life. The mean fentanyl infusion rate to achieve adequate sedation increased steadily during the 6-day infusion period, with a parallel increase in mean plasma fentanyl concentration. These data suggest that a marked tolerance to the sedative effects of fentanyl occurs in the early neonatal period, and probably reflect opioid receptor desensitization rather than an alteration in pharmacodynamics as a consequence of maturation.[2] Fentanyl may be a beneficial agent for use as a short-term sedative or analgesic in neonates undergoing ventilation, but we need a clearer understanding of its pharmacodynamics.

ALFENTANIL

Alfentanil is an analogue of fentanyl with 10–20% of its potency and a shorter duration of action.[54] Alfentanil is seldom used as an adjunct to anaesthesia in neonates but, because of its favourable pharmacokinetic properties, it is used as a sedative and analgesic in neonatal intensive care.

All data on the pharmacodynamics of alfentanil have been derived from a study of premature neonates undergoing ventilation in the intensive care unit. Twenty premature neonates (gestation 25–36 weeks, ages less than 24 h), undergoing ventilation for respiratory distress received a dose of alfentanil 20 $\mu g\ kg^{-1}$ i.v. over 2 min which produced a rapid and significant decrease in heat rate and arterial pressure and an accompanied decrease in Pa_{O_2}.[52] The same dose, in a matched age group, was noted to result in a "transient" decrease in arterial pressure, heart rate and arterial oxygen tension.[53]

Observing the use of alfentanil before treatment procedures in 20 critically ill neonates undergoing mechanical ventilation, a mean dose of 11.7 (range 9–15) $\mu g\ kg^{-1}$ produced severe muscle rigidity and jerking in four babies which impaired ventilation. EEG recordings of three of these babies showed no increase in seizure activity. Nine babies had mild to moderate rigidity which did not interfere with mechanical ventilation. It was concluded that alfentanil should not be used in neonates without neuromuscular block because of the danger of rigidity.[60]

SUFENTANIL

Sufentanil is another synthetic opioid, a thienyl analogue of fentanyl. It possesses 5–10 times the potency of fentanyl because of a greater affinity for opioid receptors.[54] Despite widespread use as an adjunct to anaesthesia in the USA, it is not as yet licensed for use in the UK. Little has been published on its use in neonates.

Some pharmacodynamic deductions were made in a comparative study of sufentanil in 28 paediatric patients. Neonates were compared with infants, children and adolescents during elective cardiac surgery. After induction of anaesthesia, a single dose of sufentanil 10–15 $\mu g\ kg^{-1}$ i.v. was given rapidly. Anaesthesia with sufentanil was supplemented with nitrous oxide or another opioid if heart rate or mean arterial pressure increased to greater than 20% of baseline values. This occurred at significantly higher plasma sufentanil concentrations in the neonatal group compared with all other groups. It was deduced that neonates may have a decreased sensitivity to the anaesthetic effects of sufentanil, or that an acute tolerance developed. However, patients more than 9 months of age received pethidine, diazepam and pentobarbitone orally as premedication 75 min before surgery, and it is likely that this had a marked effect on the analgesic efficacy of sufentanil.[23]

Conclusions

Although care must be taken in extrapolating data from animals to humans, our knowledge of opioid system development in human neonates has been enhanced by information from animal experiments. Analgesic pathways are anatomically and functionally different in the neonatal compared with the adult rat and display a marked plasticity. Although opioid systems appear very early in fetal life they do not reach adult levels of function for some time. In addition to a contribution to analgesic mechanisms, they probably have other significant roles such as regulation of neuronal development within the CNS.

There is now overwhelming clinical evidence that neonates react adversely to a noxious stimulus, although the extent of their perception of pain in comparison with adults is as yet unknown. This information has prompted a widespread increase in the use of opioids for sedation and treatment of postoperative pain, although our knowledge of their effects in this age group is still far from complete. In particular, too few studies have examined the analgesic potency of opioids in the newborn, and we are ignorant of the longer term consequences of early opioid administration on the ontogeny of opioid systems and subsequent neurological development in humans. Information from animal experiments allows us an insight into possible mechanisms in humans, but the degree to which they can be compared can only be established by a careful analysis of the developmental regulation of opioid function in human infants.

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SHORT COMMUNICATIONS

Prevention of hypothermia by cutaneous warming with new electric blankets during abdominal surgery†

Y. CAMUS, E. DELVA, A. E. BOSSARD, M. CHANDON AND A. LIENHART

Summary

We have evaluated the efficacy of new electric warming blankets, which meet the requirements of the international standard for perioperative electrical and thermal safety, in preventing intraoperative hypothermia. We studied 18 patients undergoing abdominal surgery, allocated to one of two groups: in the control group, there was no prevention of intraoperative hypothermia (n=8) and in the electric blanket group, two electric blankets covered the legs and upper body (n=10). Anaesthesia duration was similar in the two groups (mean 201 (SEM 11) min), as was ambient temperature (20.5 (0.1)°C). Core temperature decreased during operation by 1.5 (0.1)°C in the control group, but only by 0.3 (0.2)°C in the electric blanket group (P<0.01). Five patients shivered in the control group compared with one in the electric blanket group (P<0.05). We conclude that cutaneous warming with electric blankets was an effective means of preventing intraoperative hypothermia during prolonged abdominal surgery. (*Br. J. Anaesth.* 1997; **79**: 796–797).

Key words
Surgery, abdominal. Equipment, warming blankets. Temperature, monitoring.

Cutaneous warming is the most effective means of preventing intraoperative hypothermia.[1] Forced-air or electric warming blankets can be used for this purpose.[2] However, until recently, the use of electric blankets was restricted because of concern over electrical hazards and thermal injuries. Electric warming blankets are now available which meet the requirements of international standards for perioperative electrical and thermal safety. The aim of this study was to evaluate the efficacy of intraoperative cutaneous warming with these new electric blankets during prolonged abdominal surgery.

Methods and results

After obtaining local Ethics Committee approval and informed consent, we studied 18 adult patients, ASA I–II. Patients were under-going non-haemorrhagic abdominal surgery in the supine position, lasting at least 2 h, under general anaesthesia. Anaesthetic gases were not actively warmed and i.v. fluids were infused at room temperature. Patients were allocated randomly to one of two groups. In eight patients (control group), no special precautions were taken to prevent hypothermia unless core temperature decreased to less than 35 °C; to avoid more profound hypothermia, cutaneous warming of the legs was then started with a lower body forced-air blanket attached to a forced-air warmer (Bair Hugger model 500E) set on high (air temperature approximately 43 °C). In the other 10 patients (electric blanket group), two electric blankets (Electro Concept) covered the available skin surface: one (model CB2, 110 x 90 cm) over the legs up to the pubis, the second (model CB3, 120 x 40 cm) over the head, trunk and arms. The two blankets were set at 40 °C and a single layer of cotton sheeting was interposed between the skin and blankets to prevent staining, as recommended by the manufacturer. The blankets were placed over the legs as soon as the patient lay on the operating table, and over the upper part of the body after tracheal intubation.

Each blanket is attached to a control box, which is connected to an AC 230 V/50 Hz wall supply. Eight thermal probes, distributed in the blanket, are connected to thermostats located in the control box. The blanket and control box meet the 1996 ISO standards regarding thermal safety, electrical safety, fire protection and mechanical characteristics. Contact skin temperature greater than 41 °C is not permitted. Leak currents in the blankets are <3 μA, although up to 5000 μA are allowed in such products. Each blanket is made of a watertight PVC sheath containing an inner viscose layer with a single electric warming component and weighs 1 kg. The blankets are sponged and disinfected with a solution of benzalkonium chloride.

Ambient temperature was measured by a thermocouple positioned at the level of the patient. Core temperature (T_{core}) was measured at the tympanic site. Skin temperatures were measured at five skin-surface sites (lateral aspect of the arm, thorax,

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Y. CAMUS, MD, E. DELVA, MD, A. E. BOSSARD, MD, M. CHANDON, MD, A. LIENHART, MD, Département d'Anesthésie Réanimation, Hôpital Saint-Antoine, 184, rue du faubourg Saint-Antoine, 75012 Paris, France. Accepted for publication: July 30, 1997.

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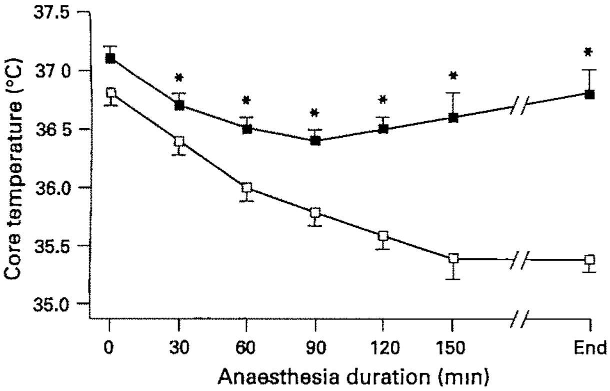

Figure 1 Intraoperative changes in tympanic temperature (mean, SEM) in the control group (□) and in electric blanket group (■). *$P<0.05$ between groups.

thigh and calf, and ventral aspect of the thigh). All temperature probes were attached to electronic thermometers (Mon-a-therm). Temperatures were recorded at 15-min intervals from induction of anaesthesia until core temperature returned to its initial value after operation. The highest skin temperature was noted. During recovery, shivering was evaluated at 5-min intervals by an independent observer blinded to the treatment. The skin was examined carefully in the recovery room for thermal lesions. Data are expressed as mean (SEM) and analysed using ANOVA, the modified *t* test, Fisher's exact test and the unpaired *t* test, as required. $P<0.05$ was considered statistically significant.

The two groups did not differ significantly in age (50 (range 24–65) yr), weight (68 (2) kg), initial core temperature (37.0 (0.1) °C), duration of anaesthesia (201 (11) min), i.v. fluids administered (1.7 (0.1) litre) or operating room temperature (20.5 (0.1) °C). Changes in T_{core} in the two groups are shown in figure 1. In the control group, T_{core} decreased during the first 3 h, then stabilized and was 35.5 (0.1) °C at the end of anaesthesia. T_{core} decreased to less than 35 °C in three of eight patients in the control group and forced-air warming of the legs was started. In the electric blanket group, T_{core} decreased during the first 90 min, but increased thereafter to reach 36.9 (0.2) °C at the end of anaesthesia. Mean T_{core} decreased during operation by 1.5 (0.1) °C in the control group but only by 0.3 (0.2) °C in the electric blanket group ($P<0.01$). The highest skin temperature registered under the blankets was 38.4 °C. During recovery, shivering was observed in five patients in the control group and in one patient in the electric blanket group ($P<0.05$). No postoperative thermal skin lesions were detected.

Comment

After an initial rapid decrease in core temperature caused by internal body heat redistribution, intraoperative core hypothermia results mainly from heat loss exceeding metabolic heat production. Intraoperative skin surface warming is the most efficient means of maintaining patients normothermic as it allows effective heat transfer to the body. For this purpose, the efficacy of both forced-air and electric warming blankets has been demonstrated. However, electric blankets involve electrical hazards as a result of insufficient electric insulation, outer sheath breakage or cutting by surgical instruments, with a risk of electrocution to the patient, surgeon or anaesthetist. Consequently, their use has generally been restricted to the recovery room. International standards (CEI 601–1; CEI 601–1–2; CEI 601–2–35) have been defined recently regarding the requirements for electrical and thermal safety of the warming devices that can be used in the operating room.

In this study, electric blankets which fulfilled these requirements significantly decreased intraoperative hypothermia during abdominal surgery. The limitation of skin warming to guarantee thermal safety could result in a lower efficacy regarding heat transfer. In a previous study, we found the use of a single blanket to be insufficient in keeping the patient normothermic during abdominal surgery.[3] The best method of improving this temperature-related restricted efficacy is to increase the amount of skin surface to be warmed. Abdominal surgery in the supine position allows cutaneous warming of the legs and upper part of the body. This combination produced sufficient heat transfer to keep patients nearly normothermic. The highest skin temperature of 38.4 °C recorded under the electric blankets was well under the limit of 41 °C allowed by international standards. In any case, such skin temperatures are not likely to produce thermal lesions, and none was observed.

Using electric blankets rather than forced-air warming can reduce the cost of intraoperative warming. If fixed costs (depreciation of the main units for a 5-yr lifespan and maintenance by the manufacturers) are similar, the cost of disposable air blankets is much higher than the labour cost of cleaning electric blankets. We estimated that warming therapy in our institution is 2–3 times less costly with electric blankets than with forced-air warming.

In summary, cutaneous warming with electric blankets offers an effective and cost efficient means of preventing intraoperative hypothermia during prolonged abdominal surgery.

Acknowledgements

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We thank Electro Concept for the loan of the electric blankets

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Hypnotic effect of i.v. thiopentone is enhanced by i.m. administration of either lignocaine or bupivacaine

M. TVERSKOY, I. BEN-SHLOMO, M. VAINSHTEIN, S. ZOHAR AND G. FLEYSHMAN

Summary

We have compared the hypnotic requirements for i.v. thiopentone alone and in combination with i.m. lignocaine or bupivacaine. Ninety women, ASA I–II, undergoing minor gynaecological surgery were allocated randomly to nine groups of 10 patients to receive thiopentone combined with i.m. lignocaine, bupivacaine or saline, respectively. Thiopentone was administered in bolus doses of 0.5 mg kg^{-1} every 30 s until loss of response to verbal command. Lignocaine and bupivacaine significantly enhanced the hypnotic effect of thiopentone in a dose-dependent manner. The maximum doses tested (lignocaine 3.0 mg kg^{-1} and bupivacaine 1.0 mg kg^{-1}) reduced the hypnotic dose of thiopentone by 39% and 48%, respectively. We conclude that if lignocaine or bupivacaine are injected into soft tissue before induction of anaesthesia by thiopentone, the i.v. dose of the latter should be modified accordingly. (*Br. J. Anaesth.* 1997; **79**: 798–800).

Key words
Anaesthetics i.v., thiopentone. Anaesthetics local, bupivacaine. Anaesthetics local, lignocaine.

The use of local anaesthetic drugs is increasing steadily as local and regional anaesthesia gains popularity and there is a growing interest in the possible interactions of local and regional anaesthesia with drugs used for general anaesthesia.[1–3] Recently, we have documented that bupivacaine-induced spinal block significantly reduced the hypnotic requirements of thiopentone, midazolam and propofol.[2 3] Interestingly, the magnitude of this effect was not uniform for all of these drugs, which suggests an effect additional to and distinct from spinal block. Earlier reports indicated that there was a systemic interaction between lignocaine and general anaesthetics which led to reduction in the requirements for general anaesthetic agents.[4 5] However, administration of either i.v. or aerosolized lignocaine was shown to have no effect on the haemodynamic response to intubation and anaesthesia.[6] The apparent dissociation between the anaesthetic interaction and haemodynamic effect suggests that factors associated with mode of administration may play a role in the degree of synergism displayed between the combined drugs.

A possible effect of local anaesthetics injected into soft tissue is modification of the requirements for general anaesthetics. Not infrequently a dose of local anaesthetic is injected to provide pain relief for surgical procedures but is either insufficient or ineffective. The anaesthetist is then faced with a patient who has already received a dose of local anaesthetic into a soft tissue location, but still has to receive general anaesthesia. The reverse sequence may also occur when regional pain control is used during and after operation. Here, there may be an additional factor in the form of sedatives (functionally related to some of the general anaesthetics) administered in addition to this analgesia. Indeed, in a recent study we found that locally administered lignocaine or bupivacaine significantly reduced the dose of propofol required for induction of anaesthesia.[7]

In order to evaluate the hypnotic interaction between the commonly used i.v. anaesthetic thiopentone and the widely used local anaesthetics lignocaine and bupivacaine, we carried out this prospective, double-blind, dose–response study.

Methods and results

After obtaining informed consent and approval from the Institutional Review Board, we studied 90 women (aged 20–50 yr; ASA I or II; weighing 50–90 kg) undergoing elective minor gynaecological surgery. Patients did not receive premedication and were allocated randomly to one of nine subgroups of 10 women each, divided further into three groups: group 1 (40 patients) received one of four doses of 4% lignocaine i.m. (0.5, 1.0, 2.0 and 3.0 mg kg^{-1}; 10 patients for each dose), administered into the gluteus muscle 10 min before induction of anaesthesia; group 2 (40 patients) received one of four doses of 0.5% bupivacaine i.m. (0.25, 0.5, 0.75 and 1.0 mg kg^{-1}; 10 patients for each dose), administered into the gluteus muscle 30 min before induction of anaesthesia. Thus the volume injected

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MARK TVERSKOY*, MD, PHD, IZHAR BEN-SHLOMO, MD, MALCA VAINSHTEIN, MD, SHIFRA ZOHAR, MD, GREGORY FLEYSHMAN, MD, Departments of Anaesthesia and Obstetrics and Gynaecology, The "Rebecca Sieff" Government Hospital, Safed, Israel. Accepted for publication: July 18, 1997.

*Address for correspondence: Department of Anaesthesia, The "Rebecca Sieff" Government Hospital, Safed, Israel 13100.

Table 1 Groups and subgroups of patients in a study on the interaction of i.v. thiopentone and i.m. lignocaine or bupivacaine. Values are mean (SD). $^*P<0.05$ compared with group 3

Group		Lignocaine dose (mg kg^{-1})	Bupivacaine dose (mg kg^{-1})	Thiopentone dose (mg kg^{-1})
1	a	0.5		4.23 (0.64)
	b	1.0		3.37 (0.30)*
	c	2.0		3.16 (0.37)*
	d	3.0		2.70 (0.41)*
2	a		0.25	4.46 (0.68)
	b		0.50	3.37 (0.42)*
	c		0.75	2.94 (0.14)*
	d		1.00	2.29 (0.47)*
3	(Controls)	0.0	0.00	4.42 (0.70)

was 1–6 ml. Intervals between i.m. injection of lignocaine or bupivacaine and i.v. injection of thiopentone were planned in the light of pharmacokinetic considerations regarding injection of these local anaesthetics to skeletal muscle or fat tissue.[8] Group 3 patients ($n=10$) served as controls and received saline 3 ml i.m. into the gluteus muscle 10 min before induction of anaesthesia.

Inability to respond to a simple command was used as the end-point for hypnosis ("open your eyes!", said twice). Thiopentone was administered i.v. over 5 s in bolus doses of 0.5 mg kg^{-1} every 30 s. Response to verbal command was evaluated 25 s after the conclusion of each bolus. The total dose required to achieve loss of response in each patient was recorded.

The physician who administered thiopentone and monitored the response to verbal command was unaware of the type or dose of local anaesthetic (or saline) administered earlier. On completion of the experimental evaluation, anaesthesia was continued and complemented with additional agents, as clinically applicable.

Analysis of variance (ANOVA) was used to evaluate the difference in mean dose for hypnosis between the subgroups of 10 patients. A simple regression analysis was used to evaluate the consistency of the trend. $P<0.05$ was regarded as the threshold for significance.

There were no differences in age or weight between the nine subgroups of 10 patients (ANOVA). No patient complained of local pain at the injection site that lasted for more than a few seconds. The mean dose of thiopentone for hypnosis in group 3 (controls) was 4.42 (SD 0.70) mg kg^{-1}. A progressive reduction in the mean hypnotic dose was noted for both lignocaine and bupivacaine (fig. 1). The lowest doses of lignocaine and bupivacaine tested (0.5 mg kg^{-1} and 0.25 mg kg^{-1}, respectively) did not reduce significantly the hypnotic dose of thiopentone. The first dose of lignocaine which significantly reduced the hypnotic dose of thiopentone was 1.0 mg kg^{-1}, and that of bupivacaine 0.5 mg kg^{-1} (table 1). The highest doses of lignocaine and bupivacaine tested in this study (3.0 mg kg^{-1} and 1.0 mg kg^{-1}, respectively) reduced the hypnotic requirements for thiopentone by 39% and 48%, respectively. When all individual values for each curve were considered, the trend in reduction of thiopentone hypnotic requirements was $r^2=0.751$ and $r^2=0.594$ for lignocaine and bupivacaine, respectively ($P=0.0001$ in both cases). Alternatively, if only the mean thiopentone dose points, corresponding to the 10 patient groups in the curve, were considered, the trends remained significant for lignocaine ($r^2=0.905$; $P=0.013$) and bupivacaine ($r^2=0.938$; $P=0.0067$).

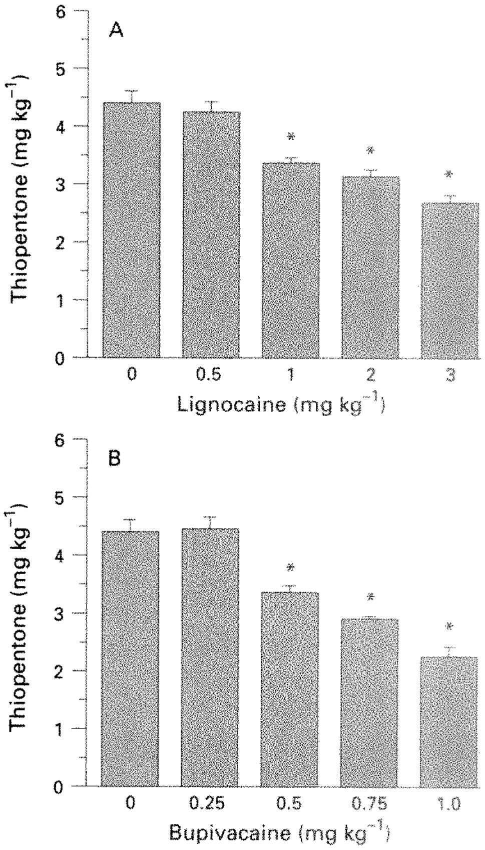

Figure 1 Enhancement of the hypnotic effect of i.v. thiopentone by lignocaine i.m. (A) or bupivacaine i.m. (B). Each point represents the mean (SEM) dose required to achieve loss of response to verbal command in a group of 10 women. $^*P<0.05$.

Comment

The hypnotic dose of thiopentone in the control group in this study (4.42 (0.70) mg kg^{-1}) was within the recommended range for induction of anaesthesia. The highest doses of local anaesthetics tested were less than half the recommended maximum clinical doses.[8] Local anaesthetics are known to have some effects on the central nervous system, which are not unlike some of those of general anaesthetics. Several earlier studies examined the interaction between lignocaine and general anaesthetics;

lignocaine was usually administered i.v. in these studies. In 1982, Kissin and McGee demonstrated that for the hypnotic effect in rats, i.v. thiopentone and i.v. lignocaine were antagonistic[9] at the ED_{50} level, while Phillips and colleagues demonstrated in human patients that lignocaine 250 mg i.v. reduced the anaesthetic dose of thiopentone by 13%.[10] More recent studies indicated that there were no haemodynamic effects for the combination of general anaesthetics and lignocaine.[6] However, these did not examine the hypnotic effect, which may be modified. The difference in magnitude of this enhancement of the hypnotic action of thiopentone, between the formerly described i.v. route of lignocaine administration and the i.m. route of injection that we used for the same drugs (i.e. 13% and 39%, respectively), may reflect a difference in pharmacokinetics between the two routes of administration. However, elucidation of the underlying cause is beyond the scope of our study.

The clinical relevance of our results lies in the growing use of local and regional alternatives for general anaesthesia. Physicians should be alert to the nature of the interaction described in this study. Recently, we found that the two local anaesthetics tested in this study interacted in the same way with propofol,[7] and we are currently investigating their combination with additional general anaesthetics.

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Effect of methohexitone and propofol with or without alfentanil on seizure duration and recovery in electroconvulsive therapy

T. T. NGUYEN, A. K. CHHIBBER, S. J. LUSTIK, J. W. KOLANO, P. J. DILLON AND
L. B. GUTTMACHER

Summary

We have studied the effects of methohexitone and propofol with and without alfentanil on seizure duration and recovery in this observer-blinded, prospective, randomized, crossover study involving 24 patients undergoing electroconvulsive therapy (ECT). Each patient had four treatment sessions, and received the following four i.v. regimens in random order: methohexitone 0.75 mg kg^{-1}, methohexitone 0.50 mg kg^{-1} and alfentanil 10 μg kg^{-1}, propofol 0.75 mg kg^{-1}, propofol 0.50 mg kg^{-1} and alfentanil 10 μg kg^{-1}. Additional methohexitone or propofol was given as needed in 10–20-mg increments until loss of consciousness. Suxamethonium 1.0 mg kg^{-1} i.v. was given for muscular paralysis. Mean motor and EEG seizure durations were longer with methohexitone–alfentanil (44.7 (SD 15.0) and 70.5 (29.7) s) than with methohexitone (37.6 (12.6) and 52.6 (15.3) s) and similarly, seizures were longer with propofol–alfentanil (36.8 (15.2) and 54.5 (20.9) s) than with propofol alone (27.2 (11.9) and 39.2 (3.9) s). Seizures were longest with methohexitone–alfentanil and shortest with propofol. Recovery time was statistically shorter in patients receiving propofol compared with methohexitone–alfentanil and methohexitone alone. Alfentanil with a reduced dose of methohexitone or propofol provided unconsciousness and increased seizure duration in patients undergoing ECT. We conclude that the combination of methohexitone with alfentanil is a good regimen for ECT, especially for patients with short seizure duration. (*Br. J. Anaesth.* 1997; **79**: 801–803).

Key words
Analgesics opioid, alfentanil. Brain, convulsions. Anaesthetics i.v., methohexitone. Anaesthetics i.v., propofol. Complications, seizures.

Electroconvulsive therapy (ECT) is a standard method for treating severe depression.[1] Methohexitone and propofol have been used to provide the brief period of unconsciousness needed for ECT[2]; however, both produce a dose-dependent decrease in seizure duration.[3] Although no studies have proved a correlation between seizure duration and clinical outcome, prolonged seizures may be more efficacious[4] and a motor seizure duration of greater than 25 s has been recommended to ensure clinical adequacy of treatment.[5] A further reduction in methohexitone or propofol dose could increase seizure duration but might not provide adequate hypnosis. Alfentanil is a rapid acting opioid with an ultrashort duration of action and no known anticonvusant effect. Combining alfentanil with propofol or methohexitone produces loss of consciousness with a smaller induction dose and thus could potentially increase seizure duration. We compared propofol and methohexitone with or without alfentanil with regard to seizure duration and haemodynamic stability after ECT.

Methods and results

After obtaining IRB approval and informed patient consent, we studied 24 patients, ASA I–III, during a series of four ECT. All patients presenting for a series of greater than or equal to four ECT were enrolled in this crossover, observer- and patient-blinded, prospective, randomized study. Non-invasive arterial pressure, heart rate, electrocardiogram (ECG) and oxygen saturation were recorded at 2-min intervals. Labetalol 20–40 mg was administered before ECT to patients with a history of hypertension. Each patient received the following four i.v. regimens of induction agents in a computer-generated random order: methohexitone 0.75 mg kg^{-1},[2] methohexitone 0.50 mg kg^{-1} with alfentanil 10 μg kg^{-1}, propofol 0.75 mg kg^{-1},[2] and propofol 0.50 mg kg^{-1} with alfentanil 10 μg kg^{-1}. Patients were assessed clinically at approximately 60 s after administration of induction agent and additional methohexitone or propofol was given in 10–20-mg increments if needed until loss of eyelash reflex and response to verbal command. Neuromuscular block

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THOMAS T. NGUYEN, MD, ASHWANI K. CHHIBBER*, MD, STEWART J. LUSTIK, MD, JEFFREY W. KOLANO, MD, PATRICIA J. DILLON, RNC, LAURENCE B. GUTTMACHER, MD, Departments of Anesthesiology and Psychiatry, University of Rochester Medical Center, Rochester, New York, NY, USA. Accepted for publication: July 22, 1997.

*Address for correspondence: University of Rochester Medical Center, Strong Memorial Hospital, Department of Anesthesiology, Box 604, 601 Elmwood Avenue, Rochester, New York 14642, NY, USA.

Table 1 Recovery room stay (PACU time) and drug doses for the four regimens (mean (SD)). $P<0.05$ compared with *methohexitone, †methoheitone–alfentanil and ‡propofol

	Methohexitone	Methohexitone–alfentanil	Propofol	Propofol–alfentanil
PACU time (min)	34.0 (88)	35.0 (6.78)	30.5 (5.46)*†	31.8 (5.70)*
Initial dose (mg kg^{-1})	0.75	0.50	0.75	0.50
Total dose (mg kg^{-1})	0.92 (0.25)	0.60 (0.18)*	1.13 (0.52)	0.76 (0.37)‡

was produced with suxamethonium 1.0 mg kg^{-1} i.v. Patients' lungs were ventilated with an air and oxygen mixture during the apnoeic phase. An arterial tourniquet was applied to the right arm of each patient to isolate the right hand for assessment of motor seizure duration. The stimulus was administered immediately after resolution of muscle fasciculations. Five patients received unilateral and 19 patients received bilateral ECT. Two frontal electrodes were placed to record continuous EEG seizure activity using a Thymatron device (Somatics Inc., Lake Bluff, IL, USA). Patients received ECT with 30–50% of the maximum output stimulus depending on the attending psychiatrist's choice. The electrical stimulus used for each patient was kept constant during the study and none required an increase in the stimulus to achieve a longer seizure duration.

EEG seizure durations were determined from the EEG recording at the conclusion of the study by a blinded psychiatrist. Duration of motor seizure was recorded as the time from the beginning to the end of tonic–clonic motor activity in the isolated hand by a nurse who was also blinded to the induction agent used. Anaesthetic dose requirements, duration of stay in the post-anaesthesia care unit (PACU), and heart rate and arterial pressure were also recorded by a blinded nurse. Patients were discharged from the PACU when they met the following criteria: stable haemodynamic and respiratory status, response to verbal commands and ability to move from bed to wheelchair. Mental status was assessed before and after ECT by the same blinded nurse every 5 min until the patient returned to pre-ECT status.

Data were analysed using repeated measures ANOVA for comparison of anaesthetic dose requirements, EEG and motor seizure duration, and duration of stay in the PACU. Data were also analysed by *post-hoc* Student–Newman–Keuls test, where appropriate. $P<0.05$ was considered significant.

Eight men and 16 women, mean age 52 (range 25–80) yr and weight 81 (SD 25) kg (range 55–160 kg) were enrolled in the study for a total of 96 ECT. The doses of methohexitone and propofol with and without alfentanil are listed in table 1. Addition of alfentanil 10 μg kg^{-1} allowed a decrease in induction dose of both methohexitone and propofol by approximately 33%. Thirteen patients (54.1%) required supplementary doses of an induction agent: 46% in the methohexitone group, 54% in the propofol group, 29% in the methohexitone–alfentanil group and 41% in the propofol–alfentanil group. Patients in the methohexitone and methohexitone–alfentanil groups required 23% and 20% increases in their initial dose, respectively, to obtain loss of eyelid reflex and response to verbal command compared with patients in the propofol and propofol–alfentanil groups who required 51% and 52% increases in their initial dose, respectively, to obtain the same response. The ratio between doses of methohexitone and propofol with and without pretreatment with alfentanil were 1:1.27 and 1:1.23, respectively.

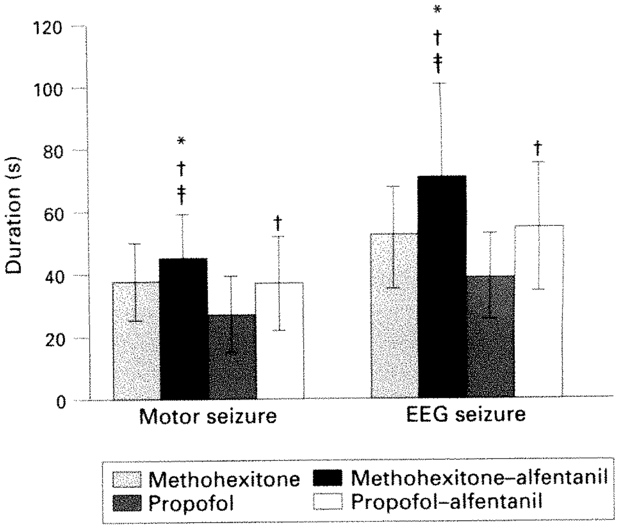

Figure 1 Mean (SD) duration of motor and EEG seizures in the four treatment groups. $P<0.05$ compared with: *methohexitone; †propofol; ‡propofol–alfentanil.

Durations of motor and EEG seizures were longest in the methohexitone–alfentanil group and shortest in the propofol group (fig. 1). Durations of EEG and motor seizures were greater when patients were anaesthetized with methohexitone or propofol in combination with alfentanil than when methohexitone or propofol alone was used (fig. 1). All EEG seizures lasted longer than 25 s except for two of the treatments, performed using propofol alone. PACU duration was significantly shorter in patients receiving propofol or propofol with alfentanil (table 1). Patient mental status (anxiety level, clumsiness, fatigue and drowsiness) at the time of discharge was not affected by the induction agent administered. Alfentanil in combination with methohexitone or propofol had no significant effect on haemodynamic stability.

Comment

Our patients undergoing ECT with reduced doses of methohexitone with alfentanil had a longer duration of EEG and motor seizures than patients anaesthetized with methohexitone or propofol alone or propofol and alfentanil combined. Propofol with alfentanil was associated with longer EEG and motor seizures than propofol alone. This increase in duration of motor and EEG seizures with the addition of alfentanil probably resulted from its additive effect leading to decreased requirements for methohexitone or propofol and the lack of effect of alfentanil on seizures.

A previous study by Weinger and colleagues demonstrated that pretreatment with fentanyl reduced seizure duration compared with a control group in patients undergoing ECT.[6] In contrast, our study demonstrated prolongation of seizure duration when alfentanil was used to decrease the induction dose of methohexitone or propofol.

The doses of methohexitone and propofol in our study were higher than the doses used by Fredman and colleagues.[2] This may be because there were younger subjects in our study requiring higher doses of anaesthetics and different end-points for loss of consciousness between the studies (loss of eyelash reflex in our study in addition to loss of response to verbal commands in Fredman's study). We could not establish a relationship between the dose of anaesthetic agent and seizure duration as there was minimal intra-patient dose variability.

The cardiovascular response to ECT is caused by activation of the autonomic nervous system. Initial parasympathetic activation results in bradycardia that is followed rapidly by sympathetically induced tachycardia and hypertension.[7] Rampton and colleagues[8] compared the cardiovascular response to ECT after administration of either methohexitone or propofol and reported improved haemodynamic stability after administration of propofol. However, in our study, there was no difference in haemodynamic stability between the four groups. The doses of methohexitone and propofol used in our study were tailored individually to achieve adequate anaesthesia for ECT and patients with a history of hypertension were pretreated with labetalol. This could explain the absence of statistical difference in MAP and heart rate between the four groups. None of the patients in all four groups developed arrhythmias or showed ECG signs of myocardial ischaemia.

The small dose of alfentanil (10 $\mu g\ kg^{-1}$) allowed prolongation of seizure duration without adverse opioid side effects such as chest wall rigidity, respiratory depression or nausea and vomiting. Dinwiddie and Isenberg used high-dose alfentanil (25 $\mu g\ kg^{-1}$) which resulted in nausea and vomiting in two of eight patients.[9]

There was a prolongation in duration of stay in the PACU in patients receiving methohexitone or methohexitone–alfentanil. This was probably a result of the increased seizure durations in these patients. Alternatively, the smooth recovery of propofol may have led to earlier PACU discharge as has been demonstrated in patients undergoing outpatient surgery.[10]

Although seizure duration may be affected by many factors such as sex, electrode placement (unilateral or bilateral), applied energy, individual seizure thresholds, previous ECT or concomitant drug therapy, the crossover design of this study should have eliminated potential bias from inter-patient variability.

In summary, using alfentanil to reduce the dose of methohexitone or propofol resulted in a longer seizure duration but no significant effect on recovery in patients undergoing ECT. Psychiatrists' opinions vary regarding the importance of seizure duration. If it is assumed that short seizures may result in reduced therapeutic benefit, then combined methohexitone and alfentanil may be a better regimen for ECT than methohexitone alone, and propofol with alfentanil is a reasonable alternative.

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Pharmacokinetics of controlled release morphine (MST) in patients with liver cirrhosis

H. I. M. KOTB, M. Y. EL-KABSH, S. E. S. EMARA AND E. A. FOUAD

Summary

We have studied the kinetic profile of controlled release morphine (MST) in 12 patients with post-hepatitic cirrhosis, caused by HCV and HBsAg, with portal hypertension, given MST 30 mg for endoscopic sclerotherapy and compared the data with those from 10 healthy controls. Plasma drug concentrations were measured in venous blood samples at intervals up to 12 h by high-pressure liquid chromatography (HPLC). Total body clearance (*Cl*) and systemic availability were estimated using a compartmental method. Patients with cirrhosis had less clearance (0.586 litre h^{-1}) than controls (0.729 litre h^{-1}). Mean residence time (MRT) was prolonged in cirrhotic patients (19.57 h) compared with controls (7.03 h). Elimination half-life in cirrhotic patients (mean 7.36 (SEM 0.45) h) was nearly twice that of controls (4.01 (0.15) h). Serum concentrations were higher at all sampling times in the cirrhotic patients (peak concentration 35.2 (3.2) ng ml^{-1} compared with 12.8 (0.4) ng ml^{-1} in controls). For these changes in the kinetic profile of morphine (as MST) in cirrhotic patients, who experienced more sedation than controls, a smaller dose study together with longer dosing intervals is recommended. (*Br. J. Anaesth.* 1997; **79**: 804–806).

Key words
Analgesics opioid, morphine. Liver, cirrhosis. Pharmacokinetics, morphine. Formulations, morphine.

Morphine is metabolized mainly by the liver and its metabolites are excreted via the kidney.[1] Therefore, it might be expected that there are alterations in morphine disposition in patients with liver disease. Investigations have shown both normal[2] and abnormal clearance[3] of i.v. morphine in alcoholic cirrhosis. It was proposed that these differences were related to the severity of hepatic dysfunction in the two groups studied. Blaschke[4] suggested that, as different types of liver disease vary in their relative emphasis on changes in liver cell function, liver blood mass and liver blood flow, so pathological differences may present as a spectrum of altered pharmacokinetics for a given drug. A drug that undergoes clearance by the liver, being mainly flow-dependent, is affected more than a capacity-limited drug under conditions in which liver blood flow is more compromised than hepatocellular function (and vice versa). However, few studies have investigated this hypothesis. Often the term "cirrhosis" has been used as a general description for patients with liver disease, irrespective of aetiology.

Sustained release oral morphine (MST continus: Napp Laboratories) has become popular as an analgesic. However, there have been no studies on its disposition in patients with cirrhosis of the liver. In this study, our aim was to define the pharmacokinetic profile of MST in a group of patients with post-hepatitic liver cirrhosis (Child's classification A and B) compared with a healthy control group.

Methods and results

Institutional approval and patient consent were obtained from 12 patients (mean age 40.3 (35–45) yr; mean weight 65.17 (SD 4.53) kg) who were admitted to the gastroenterology unit of Assiut University Hospital for endoscopic sclerotherapy of oesophageal varices. All were cirrhotic as a result of previous hepatitis C (HCV) or B (HBV) infection. All had normal renal function with normal serum creatinine concentration. None was receiving drugs known to alter hepatic blood flow or hepatic metabolizing enzyme ability and none had previously received morphine or other opioids.

To ensure homogeneity in the cirrhotic patients, serum albumin, serum bilirubin and total protein concentrations were all within the normal range; the albumin to globulin ratio was lower than normal. None of the patients had surgical portocaval shunts and none had clinical evidence of ascites.

The control group comprised 10 fasting healthy subjects (mean age 39.3 (range 35–45) yr; mean weight 65.0 (SD 1.94) kg) with normal hepatic and renal function tests, and negative hepatitis (anti-HCV and BsAg) tests.

Both groups received MST oral morphine 30 mg

HASSAN I. M. KOTB, MD (Departments of Anaesthesia); MOHAMED Y. EL-KABSH, MD (Department of Clinical Pathology, Faculty of Medicine); SAMY E. S. EMARA, PHD, (Department of Pharmaceutical Analytical Chemistry); EHAB A. FOUAD, PHD (Department of Pharmaceutics, Faculty of Pharmacy) Assiut University Hospital, Assiut, Egypt. Accepted for publication: March 26, 1997.

Correspondence to H. I. M. K.

and a cannula was inserted into an antecubital vein under local anaesthesia to facilitate sampling of venous blood. Blood was obtained every 30 min for the first 3 h, followed by every hour for the next 3 h, and then every 2 h up to 12 h. Serum concentrations of morphine were measured by high-pressure liquid chromatography (HPLC). Plasma (0.2 ml) was deproteinized with acetonitrile 0.2 ml, and then a portion (50–100 μl) of the supernatant was analysed on an ODS/TM column with a mobile phase of (ml min^{-1}) acetonitrile–methanol–phosphate buffer (20:20:60), pH 6.6 and 0.3% ethylamine. The fluorescence response was measured at excitation and emission wavelengths of 215 and 348 nm, respectively. The limit of quantitation was 2 ng ml^{-1}, with a coefficient of variation of less than 3%.

Data at different times after oral MST 30 mg were fitted to a two-compartment model, and total body clearance and bioavailability were measured. The differential equations of the proposed model were analysed using the MULTI (Runge computer) program.[5]

It was assumed that the steady state volume of distribution (V^{ss}) was almost the same in the two groups, as reported by Mazoit and colleagues.[3] Other variables, including maximum concentration in blood ($C_P$max), and time to reach maximum concentrations (tC_Pmax), were obtained graphically. The linear trapezoidal method was used for determination of the area under the plasma–concentration curve (AUC) and the area under the first moment curve (AUMC) for determination of mean residence time (MRT). The half-life of the elimination phase ($T_{1/2}$) was calculated using the slope of the elimination phase: $T_{1/2}{}^{\beta}=0.693/\beta$.

Plasma concentrations of morphine over the 12-h study are shown in figure 1. There was rapid appearance of morphine in blood within the first 30 min of the study in both controls and cirrhotic patients. In controls, the curve showed a decreasing trend after 5 h of sustained plasma concentrations with no secondary peak. A higher peak was reached in cirrhotic patients with a sustained concentration almost above that in controls over the study period. This decay in serum morphine concentration showed biexponential decay in both groups.

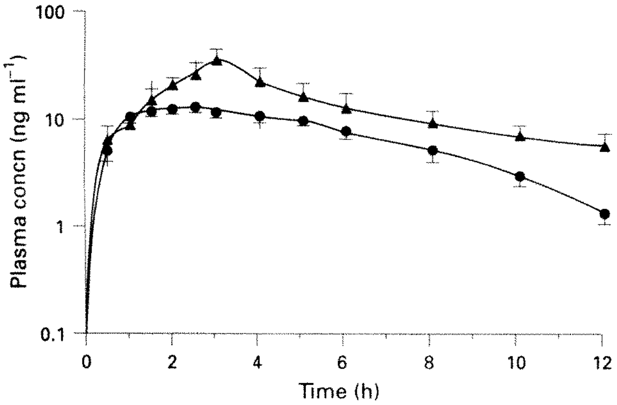

Figure 1 Semi-logarithmic curves representing plasma concentrations of morphine after administration of oral MST 30 mg to normal (●) and cirrhotic patients (▲) (mean, SD).

Table 1 Pharmacokinetics of morphine in normal and cirrhotic patients after oral MST administration (mean (SEM)). All results were significantly different between control and cirrhotic patients (Student's *t* test, $P<0.05$). *These variables were calculated using mean data

Variable	Control oral MST	Cirrhotic oral MST
$C_P$max (ng ml^{-1})	12.81 (0.47)	35.21 (3.24)
tC_Pmax (min)	142.50 (4.91)	174.0 (3.33)
AUC (μg h^{-1} litre^{-1})	92.56 (3.85)	221.33 (33.01)
MRT (h)	7.03 (0.61)	19.57 (0.19)
$T_{1/2}$ (h)	4.01 (0.15)	7.36 (0.45)
*F (%)	16.0	27.7
*Cl (litre h^{-1} kg^{-1})	0.729	0.586

There were significant differences ($P<0.05$) for all kinetic variables studied between the cirrhotic patients and normal subjects (table 1). Cirrhotic patients were over sedated and experienced more side effects than controls.

Comment

We have determined the pharmacokinetics of oral MST 30 mg in normal subjects and cirrhotic patients. Derived kinetic variables in control subjects fitted closely with those reported previously.[6 7]

Patients with severe stable liver cirrhosis, with portal hypertension secondary to viral C and B inflammation, were studied. They received oral MST 30 mg for endoscopic sclerotherapy and showed a three-fold increase in peak concentration of morphine resulting from the reduction in first pass metabolism secondary to reduction in liver cell mass; this led to an increase in the total systemic bioavailability of morphine from 18% in controls to 27.7% in cirrhotic patients. Portosystemic shunting increases the bioavailability of drugs that undergo first-pass effects in the liver. If this is associated with a decrease in hepatic clearance, this may augment the area under the curve and therefore caution is required in administering drugs with first-pass effects to patients with cirrhosis.

In this study, elimination half-lives and total body clearance were significantly altered in cirrhotic patients compared with controls. This clearly reflected the degree of sedation in the cirrhotic patients; however, none developed encephalopathy.

Of particular importance for an oral drug such as MST is the prolonged elimination half-life which depends on total body clearance if repeated doses of the drug are given, as accumulation is more likely to occur. Therefore, for cirrhotic patients who are given MST, a smaller dose together with a more prolonged frequency of administration is recommended.

Acknowledgement

We thank Professor Mahmoud A. Aly for advice and support.

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CASE REPORTS

Subclavian aneurysm causing brachial plexus injury after removal of a subclavian catheter

F. M. WALDEN

Summary

The use of central venous catheters is associated with many different complications, some of which can be life threatening. Most complications associated with the use of central venous catheters are either immediate and occur around the time of catheter insertion, or are delayed and are related to the duration of catheter use. Complications occurring after removal of central venous catheters are reported infrequently but are still a cause of significant morbidity. The following case report illustrates a serious complication which occurred after a large gauge central venous catheter was removed from a patient and demonstrates the importance of close observation not only at the time of catheter placement but also when such devices are removed. (*Br. J. Anaesth.* 1997; **79**: 807–809).

Key words
Complications, subclavian aneurysm. Equipment catheters, central venous. Complications, brachial plexus injury.

Brachial plexus injury is a recognized complication arising from insertion of central venous cannulae. This is not surprising in view of the proximity of the brachial plexus to the subclavian and internal jugular veins and the "blind" puncture technique which is almost universally used. The following case report describes a brachial plexus injury which occurred after removal of a well functioning subclavian catheter which had been inserted uneventfully.

Case report

A 72-yr-old female required plasma exchange for treatment of myasthenia gravis. A triple-lumen 12-French gauge dialysis catheter was inserted under local anaesthetic into the left subclavian vein using the Seldinger technique. The operator (ICU senior registrar), who was experienced in the technique, reported no difficulties during insertion of the catheter and a chest x-ray confirmed a satisfactory position; at no time was there any suggestion of arterial puncture. Intermittent plasma exchange was performed for 6 days during which time the dialysis catheter functioned well.

The catheter was removed by cutting the anchoring sutures and applying gentle traction. Eight hours later the patient complained of left shoulder pain and on examination had a swelling in the left suprascapular region which extended to the left side of the neck. Within 2 h the patient had lost power and tendon reflexes in her left arm.

A magnetic resonance imaging scan showed a mass lesion in the region of the left subclavian artery and compression of the brachial plexus (fig. 1). An angiogram (fig. 2) demonstrated this mass to be a false aneurysm arising from the subclavian artery. The patient underwent urgent surgical repair of the false aneurysm and was discharged home 10 days later, still with residual arm weakness.

Discussion

The use of central venous catheters is associated with a complication rate of 4–35%.[1] Therefore, it is always important to weigh the potential benefits of central venous cannulation against these known risks.[2] Venous dialysis catheters and other large gauge venous access devices are used with increasing frequently in modern day anaesthetic and intensive care practice. Insertion of such devices which are normally only used for sick patients is a highly specialized skill and should be reserved for experienced operators if the complications ascribed to such devices are to be minimized.[3]

Arterial complications occurring after removal of central venous catheters include arteriovenous fistulae[4 5] and vertebral artery aneurysm.[6] These have occurred several days after removal of the catheter and after difficult insertions. A subclavian aneurysm developing immediately on removal of a dialysis catheter has not been described previously, nor has brachial plexus damage caused by such an aneurysm expanding. This case is also unusual in that the aneurysm occurred after uneventful insertion, after 6 days of satisfactory use and immediately after removal.

Arterial damage caused by central venous cannulation is well recognized, the majority of these complications occurring at the time of insertion.[7] However, complications occurring after removal of central venous catheters, while being less common,

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F. M. WALDEN, BSC(HONS), MB, BS, FRCA, Department of Anaesthesiology, Royal Brisbane Hospital, Brisbane Q 4029, Australia. Accepted for publication: July 16, 1997.

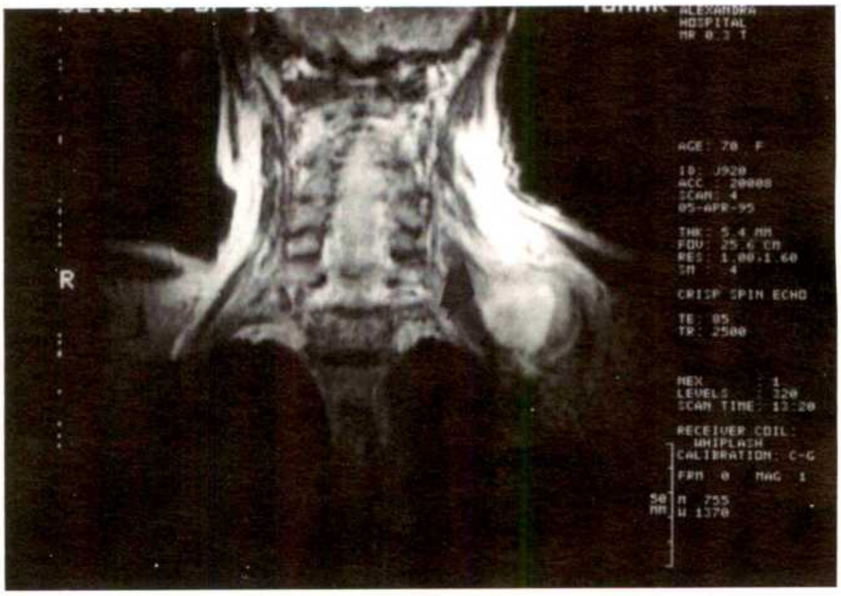

Figure 1 Magnetic resonance imaging scan of the left shoulder illustrating (arrow) 5 cm mass lesion in the left supraclavicular fossa.

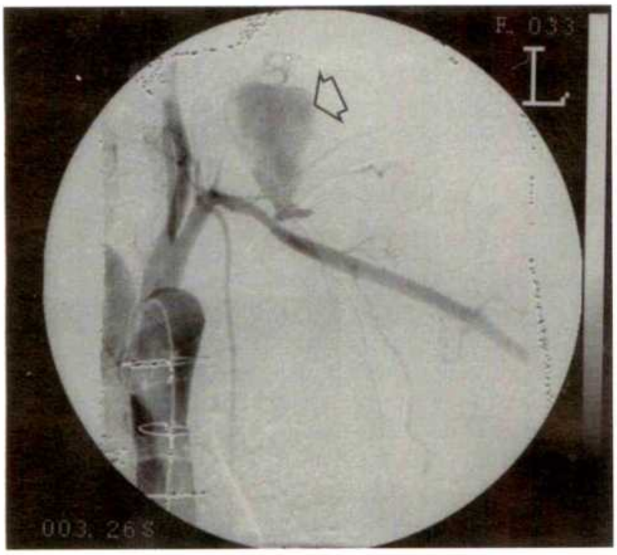

Figure 2 Arch aortogram demonstrating the false aneurysm, 4 cm in diameter (arrow), arising from the left subclavian artery, 4 cm distal to the origin of the vertebral artery.

are still a source of significant morbidity.[8 9] Unlike the current case report, late complications have usually followed difficult insertion and have occurred several days after the catheter was removed. Brachial plexus damage has been reported previously as being caused from direct trauma to the nerves by the insertion needle, guidewire or cannula, or indirectly from expanding haematomas as a result of accidental arterial puncture at the time of insertion.

Because the catheter had functioned well up until the time of removal, it is unlikely in this case to have migrated from the subclavian vein into the artery during use. While many explanations can be proposed, we postulate that it is likely that damage had occurred to the arterial adventitia during insertion or use which was not apparent so long as the catheter had remained *in situ* because of a "tamponading" effect by the catheter on the damaged artery. Only on removal of the catheter and release of the "tamponade" did the integrity of the arterial wall fail resulting in aneurysm formation. Such damage to the adventitia would not have been apparent at the time of insertion because the arterial lumen was not entered and could have occurred either from grazing of the artery by the insertion needle or guidewire, or from rubbing of the catheter on the arterial adventitia during its use.

Complications of central venous cannulation are sought and excluded at the time of catheter insertion and use, by routine chest x-ray after insertion and at intervals thereafter, frequent use of ECG monitoring and close nursing observation of the patient, catheter site and position. Late complications such as infection and catheter migration are similarly well detected and reported. It is of interest however that complications[4–6] after removal of central venous catheters are infrequently, if ever, reported. This may be in part because such complications are not so aggressively sought (and therefore are less frequently detected), despite the significant morbidity associated with such complications, as demonstrated by this and other case reports.[8 9]

This report highlights the fact that removal of central venous catheters is associated with complications, as is their insertion. We recommend a period of close observation and examination of each patient after removal of such devices.

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Anaesthesia for laparoscopic cholecystectomy in a patient with Eisenmenger's syndrome

M. S. SAMMUT AND M. L. PAES

Summary

We describe the management of a patient with Eisenmenger's syndrome presenting for laparoscopic cholecystectomy. Of prime concern was maintenance of systemic vascular resistance and this was achieved using infusion of noradrenaline started before induction of anaesthesia and continued after operation. Avoidance of other factors that could potentially increase right to left shunt flow contributed to the successful outcome. (*Br. J. Anaesth.* 1997; **79**: 810–812).

Key words
Complications, Eisenmenger's syndrome. Anaesthesia, general. Surgery, laparoscopy.

In 1897, Eisenmenger first described post-mortem evidence of pulmonary vascular disease in the presence of a large ventricular septal defect and right ventricular hypertrophy.[1] This became known as Eisenmenger's complex. The syndrome was redefined in 1958 by Wood to imply pulmonary hypertension at the systemic level caused by high pulmonary vascular resistance with reversed or bidirectional shunt via a large ventricular septal defect.[2] The actual position of the shunt is immaterial. Indeed, Eisenmenger's syndrome includes any condition in which communication between the pulmonary and systemic circulations gives rise to pulmonary vascular disease causing a right to left shunt.[3] Surgical correction of the original defect merely exacerbates the pulmonary hypertension and may precipitate right ventricular failure.

With improved management of congenital cardiac disease, Eisenmenger's syndrome is becoming very rare. However, these patients occasionally present for incidental non-cardiac surgery. We describe the successful management of a patient with this syndrome presenting for laparoscopic cholecystectomy.

Case report

A 46-yr-old woman was scheduled for laparoscopic cholecystectomy. Cardiac catheterization at 5 yr of age revealed a small ventricular septal defect (VSD) and severe pulmonary hypertension, greater than systemic pressure. In the following years she was admitted on several occasions with pulmonary infections which were treated without mishap. Cardiac catheterization at 26 yr of age showed a VSD with severe pulmonary hypertension and a right to left shunt. The main pulmonary artery pressure was 116/70 mm Hg, aortic pressure was 110/80 mm Hg and pulmonary vascular resistance was approximately 85% of the systemic level. With the patient breathing 100% oxygen, pulmonary vascular resistance decreased by 50% but right ventricular and pulmonary arterial pressures remained unchanged. A year later she underwent a full-term pregnancy with forceps delivery under extradural analgesia and was later transferred to the regional cardiac unit for post-partum monitoring. Apart from a few episodes of desaturation that responded to fluid replacement, recovery was uneventful.

She was in full-time employment at the time of surgery and was not receiving any medication apart from analgesics for gall bladder pain. She complained of shortness of breath on climbing stairs but could manage decorating her own house. On examination she was slim, not obviously cyanosed and showed no clubbing. She had no signs of increased jugular venous pressure, heart rate was 80 beat min^{-1} and arterial pressure was 120/80 mm Hg. There was right ventricular lift, and auscultation revealed a grade III systolic murmur and loud second sound. The lungs were clear. Preoperative echocardiogram showed a hypertrophied right ventricle with good function and a right to left shunt through a small VSD. The electrocardiogram showed right axis deviation with a right ventricular strain pattern and occasional ventricular ectopic beats. Preoperative chest x-ray was reported as normal.

The operation was scheduled for the afternoon and diazepam 10 mg was given in the morning as premedication. Antibiotic prophylaxis for endocarditis included teicoplanin 400 mg and gentamicin 80 mg as she was allergic to penicillin. Heparin was given subcutaneously and continued twice daily.

On arrival in the anaesthetic room, peripheral oxygen saturation (Sp_{O_2}) was 90% breathing air.

M. S. SAMMUT, MRCP, FRCA, FFARCSI, M. L. PAES, FRCA, Department of Anaesthesia, Freeman Hospital, Freeman Road, High Heaton, Newcastle upon Tyne NE7 7DN. Accepted for publication: July 16, 1997.

This was similar to values measured previously on the ward. Breathing oxygen 5 litre min^{-1} via a face mask, this increased to 99%. Midazolam 2 mg was given and direct arterial and central venous pressure monitoring was established. Before induction, an infusion of noradrenaline 0.05 μg kg^{-1} min^{-1} was started. Fentanyl 100 μg and etomidate 18 mg were used to induce anaesthesia and neuromuscular block was achieved with vecuronium. Anaesthesia was maintained with 1–2% enflurane and oxygen enriched air ($F_{I_{O_2}}=0.4$) and additional doses of fentanyl to a total of 250 μg.

Shortly after transfer to theatre, arterial pressure decreased from 130/80 to 95/40 mm Hg with a decrease in oxygen saturation to 94%. Infusion of noradrenaline was increased to maintain systemic pressure. There appeared to be a direct correlation between systemic pressure and oxygen saturation and it was necessary to maintain arterial pressure at 160/90 mm Hg to keep oxygen saturation greater than 97%. When surgery was underway this was achieved with low doses of noradrenaline (range 0.03–0.1 μg kg^{-1} min^{-1}). The increase in end-tidal carbon dioxide after pneumoperitoneum was countered by increasing the frequency of ventilation rather than tidal volume. Intra-abdominal pressure was maintained at less than 15 mm Hg and a head up tilt of 10° was allowed.

Surgery was uneventful and on completion neuromuscular blocking agents were antagonized with neostigmine and glycopyrronium. The trachea was extubated and she was transferred to the intensive care unit, as planned, for postoperative monitoring. The noradrenaline infusion was weaned gradually to a small maintenance dose of 0.03 μg kg^{-1} min^{-1} and this was eventually stopped 20 h later when she was discharged to the surgical ward. Postoperative analgesia was provided by morphine i.v. using a patient-controlled delivery system (PCA). Unfortunately, this was responsible for an episode of hypoxaemia and hypercapnia during the first postoperative night after which non-steroidal analgesic agents and paracetamol were used instead.

During walking she complained of shortness of breath on minimal exertion. These episodes were accompanied by decreases in $S_{P_{O_2}}$, as indicated by pulse oximetry, and responded to oxygen by face mask. Her postoperative haemoglobin concentration was noted to have decreased to 8.9 g dl^{-1} from a preoperative concentration of 17.2 g dl^{-1}. This was most likely the result of slow persistent blood loss from the raw gall bladder bed. Plasma-reduced blood 2 u. were transfused and symptoms improved. She was discharged home 2 days later, 8 days after operation.

Discussion

The theoretical risks of anaesthesia in patients with Eisenmenger's syndrome are considerable. The dangers of a decrease in systemic vascular resistance and subsequent increase in right to left shunt are well described. However, it has also been suggested that these patients do well with a variety of techniques.[4] Nevertheless, there is agreement that the cornerstone of safe anaesthesia in such patients is maintenance of preoperative levels of systemic vascular resistance.[5] Bird and Strunin anticipated the almost inevitable decrease in systemic vascular resistance at induction by administering a small dose of metaraminol during preoxygenation. Unfortunately, this led to hypertension and bradycardia followed by a sudden decrease in oxygen saturation remedied by administration of atropine.[6] To avoid this we opted for a noradrenaline infusion which provided easy and accurate control of arterial pressure, especially important during different levels of surgical stimulation.

The uninterrupted feedback provided by direct intra-arterial pressure monitoring was essential but we decided not to use a pulmonary artery flotation catheter. We reasoned that the risks of misdirection into the left ventricle and cardiac arrhythmias outweighed the possible benefits in this particular case given the general condition of the patient and good biventricular function identified by echocardiography. The site of communication between the pulmonary and systemic circulations also implied that the data obtained could have been misleading.[5]

An opioid-based premedication has been shown to be safe[4] but we chose a benzodiazepine to avoid the risk of preoperative respiratory depression, hypoventilation and hypoxaemia which might have precipitated a cyanotic crisis. On arrival in the anaesthetic room, $S_{P_{O_2}}$ was 90% but delivery of oxygen by a simple face mask with a flow of 5 litre min^{-1} improved this to 99%. Hypoxaemia caused by right to left shunt is not usually reversible by oxygen therapy. Although pulmonary hypertension in this patient was greater than systemic levels, the improvement in $S_{P_{O_2}}$ may be explained by a vasodilator response of the pulmonary vasculature to oxygen with improvement in pulmonary arterial flow and decreased flow across the shunt. This had been demonstrated previously during cardiac catheter studies when this patient was 26 yr old. We were somewhat surprised that this element of reversibility had been maintained.

Problems associated with anaesthesia for laparoscopic procedures pose a higher risk in patients with Eisenmenger's syndrome. Insufflation of the peritoneal cavity with carbon dioxide causes an increase in end-tidal carbon dioxide Acidosis, arrhythmias and hypotension may follow, all of which can precipitate a shunt crisis. Equally, efforts to maintain normocapnia are often accompanied by increased pulmonary airway pressures, particularly as intra-abdominal pressure increases. The effect of this is to increase pulmonary vascular resistance further. The situation may be made worse if the Trendelenburg position is adopted during surgery. Fortunately, a slight head-up tilt is often the requirement for cholecystectomy, as in this case. Other possible complications associated with this type of surgery include pneumothorax and gas embolism. The latter is particularly important because of the direct route available, via the shunt, to the systemic circulation.

Early tracheal extubation in these patients is preferable because of the deleterious effect of positive pressure ventilation, and intraoperative analgesia is thus best provided by short-acting opioids. Although it is not our usual practice to provide patient-controlled analgesia after laparoscopic cholecystectomy we felt that it was justified in this patient in order to mimimize stress in the early postoperative period. We were disappointed that it marred an otherwise uneventful immediate postoperative phase and wonder if the intensive care setting may have encouraged over zealous use of the PCA system with subsequent respiratory depression.

The increase in exertional dyspnoea noted after operation seemed to be directly related to the decrease in haemoglobin concentration. The fact that symptoms resolved after transfusion strengthened that view. The pathophysiology involved, however, is more contentious. In non-cardiac patients acute anaemia is associated with a decrease in the oxygen carrying capacity of the blood and an initial decrease in oxygen flux. The resultant tissue acidosis causes compensatory peripheral vasodilatation and increase in cardiac output. Anaemia may also contribute to a decrease in blood viscosity which reduces further peripheral vascular resistance.[7] In patients with Eisenmenger's syndrome the dynamics are inevitably more complex. Unfortunately, without the benefit of further invasive investigation in this patient the relative importance of these mechanisms and their effect on flow across the shunt remain speculative.

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CORRESPONDENCE

Ropivacaine test dose in extradural anaesthesia

Morton and colleagues[1] have described the use of 0.75% ropivacaine for extradural anaesthesia, and in the process have clearly demonstrated the unsuitability of this agent as a test dose. The aim of an extradural test dose is to identify inadvertent i.v. or intrathecal catheter placement. It should have high sensitivity, but produce symptoms that are safe. Morton and colleagues inadvertently administered large i.v. doses of ropivacaine to two patients, despite negative test doses of ropivacaine 22.5 mg. This is not surprising, as Scott and colleagues[2] gave 10 mg min^{-1} i.v. for up to 15 min before producing symptoms. We do not, however, suggest the use of a larger dose of ropivacaine as a test dose. While this may increase sensitivity in identifying vascular cannulation, dangerously high spinal anaesthesia may result in intrathecal injection. Wahedi, Nolte and Klein[3] have produced safe spinal anaesthesia with 0.75% ropivacaine 22.5 mg in non-pregnant subjects, but there are no data to clarify a safe maximum intrathecal dose of ropivacaine in the obstetric population.

The most sensitive pure local anaesthetic test dose for identifying intravascular injection of which we are aware is lignocaine 1 mg kg^{-1}, proposed by Michels, Lyons and Hopkins.[4] However, Richardson and Wissler[5] described abrupt and life-threatening high spinal block after intrathecal test doses of only 45 mg of lignocaine in two patients. Michels' test dose is therefore clearly potentially dangerous.

In summary, we suggest that it is not possible to use a pure local anaesthetic test dose of sufficient dosage to identify the intravascular space without producing dangerously high spinal anaesthesia if injected intrathecally. We see no alternative but to use separate agents to identify inadvertent intravascular or intrathecal injection. Intrathecal catheter placement can be excluded easily using bupivacaine 10 mg. We remain unconvinced of the sensitivity and specificity of adding adrenaline to this test dose, and indeed have some concerns over its safety. Perhaps the addition of a potent short-acting opioid such as remifentanil warrants some investigation in this role? The final logical but somewhat cumbersome suggestion is to follow a negative intrathecal test of bupivacaine with a second test of lignocaine 1 mg kg^{-1}.

M. DRESNER
M. ADAMS
H. KLEIN
Department of Anaesthesia
Leeds General Infirmary
Leeds

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Sir,—We thank Drs Dresner, Adams and Klein for their interest in our article. We agree that ropivacaine 22.5 mg is an unsuitable test dose and we should have given greater emphasis to this in our article. But we do not think that this could have been predicted by the work of Scott and colleagues.[1] Our test dose was given over 20 s, considerably faster than the 10 mg min^{-1} used by Scott and colleagues. We do not agree that intrathecal catheter placement can be *easily* (our italics) excluded with bupivacaine 10 mg. Prince, Shetty and Miles[2] compared plain bupivacaine 8 mg by the subarachnoid and extradural routes, and could only discriminate reliably between the two routes by testing straight leg raising after 10 min. We do not agree with the suggestion of adding remifentanil to the test dose; this would seem to be exchanging the known risks and limitations of current test doses for the unknown.

Our own routine practice is to use lignocaine 80 mg as a "test dose". It is our opinion that this dose, if given rapidly, elicits symptoms of early systemic toxicity. We acknowledge that the addition of adrenaline 1 in 200 000 may increase sensitivity and specificity. The potential for high subarachnoid block is real but at least there is early clear evidence of inadvertent subarachnoid placement of the catheter. The crucial point about test doses, and one we continually emphasize to our trainees, is that a complacent attitude to a negative test dose is dangerous; a negative test dose does not completely exclude misplacement of the catheter. When an aspiration test and a test dose are negative, large doses of local anaesthetic must still be given slowly. We believe that this, and the lower toxicity of ropivacaine compared with bupivacaine, is why the two patients in our study who received accidental i.v. injections did not come to serious harm.

C. P. J. MORTON
J. H. MCCLURE
Department of Anaesthetics
Royal Infirmary of Edinburgh NHS Trust
Edinburgh

1. Scott DB, Lee A, Fagan Bowler G, Bloomfield P, Lundh R. Acute toxicity of ropivacaine compared with bupivacaine. *Anesthesia and Analgesia* 1989; 69: 563–569.
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Use of inhaled nitric oxide in the critically ill

Sir,—We read with interest the article by Cuthbertson, Stott and Webster on the increasing use of inhaled nitric oxide (iNO) in the critically ill.[1] We would disagree with their statement that there is no evidence that iNO improves patient outcome. One study in neonates with persistent pulmonary hypertension[2] demonstrated a reduction in the need for extracorporeal membrane oxygenation (ECMO) from 71% of patients in the control group to 40% in those receiving iNO (P=0.02). There was no difference in mortality between the two groups (7.1% in the control group *vs* 6.6% in the iNO group). A study of iNO in neonates with hypoxic respiratory failure[3] also demonstrated a decrease in the use of ECMO from 54.5% in controls to 38.6% in those receiving iNO (P=0.014). Again, mortality was similar (16.5% in the control group *vs* 14% in the iNO group). ECMO is expensive, invasive and unavailable in many centres. It is associated with morbidity, but has been shown to reduce mortality in term neonates with respiratory failure.[4] Using iNO to reduce the use of ECMO would seem appropriate. The children involved in studies of iNO are assessed neurodevelopmentally at 18–24 months, which may provide further support for the use of iNO. We accept that it would be wrong to extrapolate the studies directly to adults, although they indicate that there is a real role for iNO, and we await studies in older children and adults to resolve the place of iNO in these groups.

NO is stored as 1000 ppm in nitrogen, an asphyxiating mixture In most units, iNO is added distally to the ventilator without oxygen monitoring. This is potentially dangerous. Providing less than 80 ppm of NO is used, as recommended by Cuthbertson, Stott and Webster, depression of $F_{I_{O_2}}$ is less than one-tenth of the administered $F_{I_{O_2}}$. This requires that the inspired NO concentration should be measured at all times, as they recommend, to ensure that no more than NO 80 ppm is given. NO is also available at varying lower concentrations for use in calibration of monitoring equipment. If a cylinder containing 200 ppm is used to provide an inspired NO concentration of 80 ppm, depression of $F_{I_{O2}}$ is 40% of the set $F_{I_{O_2}}$

We consider that the risks of administering a hypoxic mixture using NO are real but they have been supplanted by concerns about only NO and the higher oxides rather than its nitrogen carrier. It is important that those who use iNO appreciate all of these risks.

C.F. Whitehead
P. Baines
Paediatric Intensive Care Unit
Alder Hey Children's Hospital
Liverpool

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Sir,—Our article was specifically on the use of inhaled nitric oxide (iNO) therapy in adults. Although the data regarding extracorporeal membrane oxygenation (ECMO) in neonates with respiratory distress syndrome and hypoxic respiratory failure are interesting, it does not change our statement that there is no evidence that iNO improves outcome.[1 2] Both studies quoted demonstrated a reduction in the requirement for ECMO but there was no change in mortality. It would be wrong to extrapolate the results in neonates to adult practice. Until further studies have been reported it would not seem appropriate to use iNO therapy merely to decrease the requirement for ECMO.

We have difficulty in understanding the points raised regarding NO delivery. Our article recommended continual monitoring of iNO therapy and a maximum dose. We did not recommend the use of any other cylinder except NO 1000 ppm in nitrogen. If the authors have 200-ppm cylinders designated for "use in calibration of monitoring equipment", we presume they would not be using them for patient care thus eliminating the danger of depression of $F\text{I}_{O_2}$ to which they refer. If iNO therapy and response to therapy are monitored closely and 1000-ppm cylinders are used, we feel that the risk of delivery of hypoxic gas mixtures is minimal.

We are pleased that Drs Whitehead and Baines are in agreement with us that the users of iNO therapy must appreciate all the incumbent risks and potential benefits. It was with this aim that we undertook our survey and made our recommendations based solely on adult practice.

B. H. Cuthbertson
S. Stott
N. R. Webster
Anaesthesia and Intensive Care
Department of Medicine and Therapeutics
University of Aberdeen
Aberdeen

1. Roberts JD, Fineman JR, Morin FC, Shaul PW, Rimar S, Schreiber MD, Polin RA, Zwass MS, Zayek MM, Gross I, Heymann MA, Zapol WA. Inhaled nitric oxide and persistent pulmonary hypertension of the newborn. *New England Journal of Medicine* 1979; **336**: 605–610.
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Management of the airway and ventilation during resuscitation

Sir,—In their recent article on the management of the airway and ventilation during resuscitation, Gabbott and Baskett mentioned an intubation aid used to confirm tracheal intubation called SCOTI.[1] I would like to point out that SCOTI (Sonomatic confirmation of tracheal intubation) was first marketed by Penlon in April 1995. This was in response to a need for a device capable of providing "instant" confirmation of tracheal intubation and against a background of ever increasing risk of litigation against anaesthetists. Although the device generated a great deal of interest, sales proved disappointing and at the end of 1996 a commercial decision was taken to discontinue marketing the SCOTI device. I believe a similar device continues to be available in the USA, although I am not aware of any devices working on a similar sonomatic principle being marketed elsewhere.

I trust this information is of interest and clarifies the current position regarding the SCOTI device.

C. Richardson
Penlon Ltd
Abingdon
Oxon

1. Gabbott DA, Baskett PJF. Management of the airway and ventilation during resuscitation. *British Journal of Anaesthesia* 1997; 79: 159–171.

Weaning: is the work of breathing via a tracheostomy tube similar to that via a tracheal tube?

Sir,—Both the editorial by Shneerson[1] and a letter by Bapat and Verghese[2] highlight interesting aspects on difficult weaning from ventilation. While agreeing fully with the main message of the letter[2] which emphasizes the advantages of cuff deflation to facilitate weaning, I have reservations about the comment made on the work of breathing in spontaneously breathing patients.

It is logical to assume that a decrease in peak intrapleural pressure to approximately -15 mm Hg from a normal value of -2.5 to -6 mm Hg while breathing normally through a tracheal tube of 9.0 mm internal diameter (id) reflects an increase in the work of breathing. But is it appropriate to extrapolate this observation and assume that a tracheostomy tube of size 8.0 or 9.0 mm id produces changes of similar magnitude? Work of breathing is dependent mainly on three factors: elastic resistance of the lung; non-elastic viscous resistance; and resistance to air flow. Increase in the work of breathing caused by airway instrumentation is generally believed to be a result of the increase in air flow resistance, even though one study could not confirm this.[3] While it is true that resistance to flow via a tube is dependent much more on internal diameter than on length, halving the length of a tube can reduce resistance by up to 50%[4] and doubling the length can double the resistance.[5] This holds true when flow is laminar. (The relationship between the length of a tube and resistance encountered is complex and there is no analogue for Poiseuille's law in the case of turbulent flow.) The length of a size 9.0 mm id tracheostomy tube is 10.5 cm (Portex, profile cuff type) compared with tracheal tubes cut at 21–24 cm. However, firm conclusions on the work of breathing in tracheostomized patients can only be made from clinical investigations, and not from simple application of mathematical formulae.

Another point worth mentioning is that if a patient starts speaking soon after deflation of a tracheostomy tube cuff without closing its external orifice, there may be a plug of mucus partially obstructing the tip of the tube. This is probably one of the causes of a dramatic improvement of any patient after removal of a tracheostomy tube or extubation!

S. K. Kodakat
Department of Anaesthetics
Worthing Hospital
Worthing

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Resistance. In: *Physics for the Anaesthetist*, 4th Edn. London: Blackwell, 1987; 240–261.
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Sir,—We appreciate Dr Kodakat's interest in our comments. The main objective of our letter was to emphasize that a tracheal tube or a tracheostomy tube increases the workload of breathing relative to the normal respiratory tract.

The peak flow rate of a normal subject at rest is 0.3–0.5 litre s^{-1}. Flow rates greater than 0.25 litre s^{-1} via a tube of less than 10.0 mm internal diameter (id) are turbulent.[1] Therefore, Poiseuille's equation which deals with laminar flow can only be used partially to deduce flow characteristics during intubation. The diameter, length, curvature and material of a tube affect its flow resistance, and thus different tracheostomy tubes, even of similar size and diameter, may have different flow resistances.[2]

To achieve normal ventilation, work is performed to overcome the elastic and frictional impedances of the lungs and chest wall. In the presence of increased resistance or decreased compliance, a greater swing in pleural pressure is required to achieve a given tidal volume, thus increasing the work of breathing.[3] Respiratory muscle fatigue does not occur during quiet breathing but develops when the ventilatory work load is increased. In patients with respiratory distress an inappropriately heightened respiratory drive places excessive stress on the respiratory muscle pump and predisposes to fatigue.[4] The peak flow in such patients could easily increase to 1 litre s^{-1}, resulting in a markedly increased flow resistance with increasing flow rate in a non-linear manner, and could add substantially to the total work of breathing.[5] In this group of patients, intrapleural pressure could even be greater than −15 mm Hg. In contrast, in patients with severe respiratory muscle weakness, changes in intrapleural pressure could be smaller. However, both groups of patients may benefit from a reduction in respiratory resistance caused by cuff deflation.

We agree that for a given patient the work of breathing through a tracheostomy tube would be less compared with an equal diameter tracheal tube. There are no comparative studies of the effect of different sized tracheal tubes or tracheostomy tubes on intrapleural pressure in patients with respiratory failure. Our comment that "changes in intrapleural pressure caused by a size 8.0 or 9.0 mm id tracheostomy tube could be similar to that of a size 9.0 mm tracheal tube" was based on these factors. It was not meant that different sized tubes or tracheostomy tubes have the same flow resistance.

P. P. BAPAT
Department of Anaesthesia
Charing Cross Hospital
London
C. VERGHESE
Department of Anaesthesia
Royal Berkshire Hospital
Reading

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Continuous intra-arterial blood-gas monitoring

Sir,—After reading the study on the usefulness of continuous intra-arterial blood-gas monitoring in patients undergoing thoracic procedures,[1] I feel it necessary to comment on some of the issues raised by the investigators.

The authors stated that the Paratrend 7 (PT7) blood-gas monitoring system has been validated by only one set of investigators in collaboration with the manufacturer. I would like to draw their attention to a multicentre study from North America[2] independently validating the PT7 system. Second, it is stated that a broad range of pH, $P\text{CO}_2$ and $P\text{O}_2$ values were not evaluated in the original studies. I would like to point out that a similar range of pH (7.1–7.57), $P\text{CO}_2$ (2.65–6.85 kPa) and $P\text{O}_2$ (8–68 kPa) values have been evaluated in an earlier study by Venkatesh, Clutton-Brock and Hendry.[3]

The accuracy of the base excess and bicarbonate calculations are a function of the algorithm built into the blood-gas analyser and the monitor and accuracy of $P\text{CO}_2$ measurement. Dissociation in accuracy between the two methods for those two variables may be a reflection of differences in the algorithm or accuracy of the $P\text{CO}_2$ measurement.

While discussing the accuracy of the PT7 and blood-gas analyser, it is stated that "the accuracy and variability of blood-gas analysers are not known exactly". Studies by Hansen and colleagues, and Metger and colleagues have clearly demonstrated the bias and precision of blood-gas analysers when measuring blood-gas tensions in blood.[4 5] The authors have alluded to several factors which influence the accuracy of blood-gas analysis. Even controlling for the factors listed, the accuracy and reproducibility of blood-gas analysers remains an issue. It must be remembered that most blood-gas analysers do not use primary quality control material such as tonometered blood. This significantly limits any conclusions which can be drawn on the accuracy of an intravascular device. While studies such as these are important, clinical outcome and cost effectiveness studies are the ones which will influence the wholesale acceptance of intravascular sensing devices.

B. VENKATESH
Critical Care Medicine
Royal Brisbane Hospital
Queensland, Australia

1. Zollinger A, Spahn DR, Singer T, Zalurando MP, Stoehr S, Weder W, Pasch T. Accuracy and clinical performance of a continuous intra-arterial blood-gas monitoring system during thoracoscopic surgery. *British Journal of Anaesthesia* 1997; **79**: 47–52.
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Sir,—I read with interest the article by Zollinger and colleagues[1] independently confirming the good clinical performance of the Paratrend 7 (PT7) multiparameter intra-arterial blood-gas monitoring system first described by this institution.[2–5] Several points raised by the article require further discussion. The authors gave the impression that the sensor may be re-calibrated when inserted into a vessel by using data from a bench top blood-gas analyser. This is incorrect. Comparison between values obtained with the PT7 and bench top analyser can be made and the original calibration curve adjusted in the light of this comparison; this is somewhat different to re-calibration. When inserted into a vessel it is not possible to recalibrate the sensor without loss of sterility. The authors also stated that the PT7 can measure blood-gas variables at 37°C or at patient (intravascular) temperature. In fact, all readings by the PT7 are made at patient (intravascular) temperature and then corrected, if required, to 37°C, as opposed to bench top analysers which measure at 37°C and correct to patient temperature. A subtle difference, but differences in the temperature correction algorithms may lead to discrepancies in displayed values.

With regard to the statistical evaluation of the data, there are three principal methods of describing relationships between continuous variables: (1) assessment of whether or not two variables are associated, that is if the values of one variable tend to be higher (or lower) for higher (or lower) values of the other variable, using the method known as correlation, presuming that at least one of the variables has a normal distribution in the study population; (2) assessment of whether the value of one variable to be predicted from any known value of the other variable, for which the technique of linear regression is used; and (3) assessment of the level of agreement between the values of the two variables by calculating the mean difference between readings (bias) and the degree of variability (precision).[6]

For the study in question it is perhaps useful to know that high (or low) values from one monitor are reflected by high (or low) values from the other. Calculation of correlation coefficients and *P* values indicates how likely it is that a high (or low) value from one monitor is reflected by a high (or low) value from the other. No information on the level of agreement between the actual values displayed can be derived from this type of analysis. The PT7 monitor is designed to measure intra-arterial blood-gas tensions, not predict the values displayed by another monitor, thus calculation of regression statistics does not provide useful information on the performance of the sensor. Thus, results from correlation statistics should be interpreted with caution in this type of study and the technique of linear regression analysis should not be used.

The conclusion that the level of agreement between HCO_3^- and base excess was relatively poor requires further comment. As part of an ongoing study in our department, 28 arterial blood samples were aspirated from patients in our intensive care unit and analysed simultaneously by a single operator using two bench top blood-gas analysers (ABL 300; Radiometer, Copenhagen, Denmark and NOVA Stat Profile Plus 9; NOVA Biomedical, Waltham, MA USA). For assessment of bicarbonate concentration and base excess, the bias between machines was -0.74 mmol litre^{-1} and -0.57 mmol litre^{-1}, respectively. The precision of these readings (1.96 SD) was 4.50 and 4.47 mmol litre^{-1}, respectively. These values are of a similar magnitude to those obtained when comparing the PT7 system with the blood-gas analyser available for the study in question.

Finally, presentation of the levels of bias and precision in the units of the variables can be misleading. For example, for the above analysis the levels of bias and precision appear almost equal. However, the normal range for bicarbonate is numerically considerably larger than base excess and if bias and precision are calculated in percentage terms a different appraisal of the level of agreement is evident. For the data on bicarbonate, bias and precision were -1.59% and 16.92%, respectively. For the data on base excess, bias and precision were -43.25% and 206.72%, respectively. Therefore, when this type of data are presented, and values for bias and precision presented in the units of measurement, percentage bias and precision should also be quoted to give a more comprehensive assessment of the level of agreement.

S. J. Graystone
Department of Anaesthesia and Intensive Care
Queen Elizabeth Hospital
University Hospitals NHS Trust
Edgbaston, Birmingham

1. Zollinger A, Spahn DR, Singer T, Zalurando MP, Stoehr S, Weder W, Pasch T. Accuracy and clinical performance of a continuous intra-arterial blood-gas monitoring system during thorascopic surgery. *British Journal of Anaesthesia* 1997; **79**: 47–52.
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Sir,—Thank you for the opportunity to respond to the comments of Dr Graystone and Dr Venkatesh on our article.[1] They highlighted some important technical aspects. During use of the intra-arterial sensor system, a correction of the Paratrend 7 (PT7) values on the basis of those obtained by *in vitro* blood-gas measurement is possible. This correction may be termed readjustment or recalibration, the difference being rather semantic. However, as described, no such correction was used in our study. This is important when rating the agreement of PT7 with laboratory *in vitro* blood-gas measurements, which is considered to be the gold standard,[2] and also when comparing results of our study with previous clinical work, where such corrections were used.[3–5]

Furthermore, we agree that the algorithms built into the PT7 monitor and the bench top blood-gas analysers are crucial for the accuracy of all calculated parameters. Both the correction for measured blood-gas values from (intravascular) patient temperature to 37°C (and vice versa) and calculation of bicarbonate and base excess rely on these algorithms. Therefore, a study on the accuracy of a new system, which provides these values, indirectly includes comparison of the algorithms incorporated in this new system with those of the *in vitro* blood-gas analyser. Interestingly, the accuracy of these calculated variables which are displayed on the PT7 monitor has not been clinically investigated previously. The conflict remains, that ". . . the clinical performance of an optode-based blood-gas monitor must be judged in comparison with the gold standard electrode-based blood gas analyzer, for which clinical performance cannot be specifically quantified".[2]

At the time of preparation of our manuscript the PT7 sensor had been validated by only one group of authors. Since then Abraham, Gallagher and Fink[5] have reported on its clinical evaluation in different intensive care units. They followed a study design different from ours with special emphasis on continuous monitoring during a prolonged period of time. However, the results of their study may have been influenced by the fact that eight different bench top analysers from two different manufacturers were used in three different institutions. Furthermore, we stated that the PT7 system had been validated for limited blood-gas ranges only. This is true, as the ranges reported by Venkatesh, Clutton-Brock and Hendry[4] do not include clinically critical values of hypoxaemia and hypercapnia. However, we had the opportunity to measure some extreme values of arterial $P\mathrm{o}_2$ (6.1 kPa) and $P\mathrm{co}_2$ (9.5 kPa) during thoracoscopic surgery.

Calculation of bias and precision is considered standard statistics for comparing this type of data.[6] In addition, linear regression analyses were performed to facilitate comparison with previous work.[7] It is important to note that both types of statistical analyses consistently revealed good agreement between PT7 derived and blood-gas analyser derived values for arterial $P\mathrm{o}_2$, $P\mathrm{co}_2$ and pH, and also consistently documented significant scattering between PT7 derived and blood-gas analyser derived values such as bicarbonate and base excess.[1]

Finally, although clinical outcome and cost effectiveness studies are lacking in many other monitoring tools currently used in anaesthesia and intensive care, we agree fully that evidence-based, outcome-related data are mandatory for general acceptance of continuous intra-arterial blood-gas monitoring.

A. Zollinger
D. R. Spahn
T. Pasch
Institute of Anaesthesiology
University Hospital Zurich
Zurich, Switzerland

1. Zollinger A, Spahn DR, Singer T, Zalunardo MP, Stoehr S, Weder W, Pasch T. Accuracy and clinical performance of a continuous intra-arterial blood-gas monitoring system during thoracoscopic surgery. *British Journal of Anaesthesia* 1997; **79**: 47–52.

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4. Venkatesh B, Clutton-Brock TH, Hendry SP. Evaluation of the Paratrend 7 intravascular blood gas monitor during cardiac surgery: comparison with the C4000 in-line blood gas monitor during cardiopulmonary bypass. *Journal of Cardiothoracic and Vascular Anesthesia* 1995; **9**: 412–419.
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The future of ethical treatment

Sir,—Drs Mohr and Kettler raised important issues in their article on the ethical aspects of resuscitation.[1] Previously published guidelines have stressed the importance of obtaining patient views in decisions on whether or not to resuscitate.[2] In one large study examining the views of the elderly on admission to hospital, 186 patients from a total of 400 were deemed mentally incompetent to complete a questionnaire satisfactorily.[3] In such cases more emphasis may be placed on the views of relatives, and with an ageing population this is likely to occur more frequently.

Experience in the USA has shown that the judicial review of continuation of "futile" end of life treatment often fails to resolve differences between medical attendants and the next-of-kin. Unfortunately, in many cases the catalyst to a decision is the health insurance provider who may cap the amount spent on such care.[4]

We must be careful that we share the load of the decision making process without overburdening patients, relatives or ourselves with what will undoubtedly be increasingly difficult ethical dilemmas as the population becomes relatively more aged.

P. J. Shirley
Department of Anaesthesia
Aberdeen Royal Infirmary
Aberdeen

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Sir,—Dr Shirley raises the issue of overburdening patients, relatives and health care providers with the decision making process in ethical conflicts. In general, physicians are obligated to help patients and their surrogates to make competent decisions. However, it is important to distinguish between true advice and the more paternalistic approach of leaving the decision to the doctor [1]

We agree that the expectations on the decision making capacity of patients and their relatives should not be over-estimated; it might be limited because of the emotional involvement and lack of medical knowledge and comprehension. In case of conflict, such as the surrogates' wishes to continue futile treatment, we have to accept the obligation and responsibility family members feel towards their relatives. However, refusal of futile treatment should not be judged as unjustified paternalism, as in some situations physicians or other health care providers have to solve dilemmas and make decisions which they cannot transfer to relatives. We feel that the concept of patient's (and surrogate's) autonomy should not be abandoned, but its value is not absolute.[3]

The question that must be answered is how to distinguish between justified and unjustified refusal of patients' or relatives' wishes.[3] The apparent dilemma might be solved by an approach summarized as clinical pragmatism: a method of assessing the relevant facts; diagnosing the moral problems; considering the options; and negotiating goals and offering an (ethical) acceptable treatment plan that coheres with agreed goals.[2] In several ethical dilemmas, a process of creative problem solving might be appropriate instead of asking the attorney to make the decisions for us.

M. Mohr
D. Kettler
Department of Anaesthesiology, Critical Care and Emergency Medicine
University of Goettingen,
Goettingen, Germany

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BOOK REVIEWS

Practical Anaesthesia and Analgesia for Day Surgery. J. M. Millar, G. E. Rudkin and M. Hitchcock. Published by Bios, Oxford. Pp. 250; indexed; illustrated. Price £19.95.

The three main authors of this 250-page paperback are practising day surgery anaesthetists whose intent is to inform the reader about "Safe selection of patients, the best anaesthetic techniques and the most effective analgesia" for patients attending a day surgery unit. They undertake this exercise in a style reminiscent of Lee and Atkinson's *Synopsis of Anaesthesia*; short pithy chapters with brief paragraphs of text and frequent use of lists and tables. Friendly "information bytes" appear highlighted on almost every page and contain the authors' interpretation of the preceding text, for example "always consider more suitable alternatives before giving morphine to day cases".

The subject matter ranges from chapters on patient selection to cost effectiveness and covers all relevant aspects of day-case anaesthesia, including drugs, techniques, sedation, PONV and analgesia, paediatrics and discharge. There is a useful chapter on anaesthesia for eight different surgical sub-specialties, each section covering anaesthetic issues, strategies for managing patients and likely problems encountered.

This is not a definitive study of anaesthesia and analgesia for day surgery but it is a very well referenced and clearly presented synopsis of the subject. The authors succeed in their intention to inform the reader of the most appropriate techniques available and provide well précised evidence for their conclusions and advice. The book can be used as a practical guide for trainees embarking on day-case anaesthesia and for those wishing to study further any particular aspect of the topics covered; each chapter concludes with an up-to-date list of references which will provide a useful starting point for their research.

The book will also be a useful addition to the day unit library and will appeal to trainees preparing for examinations. Its style and clear presentation make the book appropriate for nursing staff and it would also provide a good description to management of the practical side of anaesthetists' duties in the day unit.

D. Raitt

MCQs and OSCEs for the Primary FRCA. E. Doyle and P. Goggin. Published by Butterworth Heinemann, Oxford. Pp 155; indexed; illustrated. Price £14.99.

New examinations elicit new books to help candidates, editors, authors and publishers. *MCQs and OSCEs for the Primary FRCA* has emerged ahead of the new Primary examination introduced by the Royal College of Anaesthetists, alongside the recent changes to postgraduate specialist medical training in the UK.

This book of questions states its objectives clearly in the introduction and achieves them well. It aims to cover a wide range of topics, give some information, prompt further reading and identify gaps in knowledge. The book is divided into five papers of 60 questions rather than 3.3 papers of 90 questions. Each paper contains questions from throughout the Primary syllabus. At the end of each paper are answers, many of which are qualified by short explanations and the occasional reference.

Before the MCQ papers there are two paragraphs of advice on how to sit an MCQ examination. They contain exactly the sensible suggestions that are forgotten so easily immediately the examination begins.

The MCQs are plentiful, but there are only seven OSCE questions. The OSCE questions have one group of related data or one illustration with a single question. Candidates will find that they will encounter a battery of structured questions relating to each station of clinical data, equipment, history taking or examination should they proceed beyond the MCQ paper in the Primary examination.

Yes this book will help candidates to prepare for the Primary FRCA multiple choice paper, *no* it has not filled the gap in the market for a book on the OSCEs, and *I do not know* if the £15.00 premium to the examination fee will make that fee more likely to be a "once only" payment.

D. J. R. Duthie

Methods in Molecular Biology, volume 83: Receptor Signal Transduction Protocols. R. A. J. Challis (editor). Published by Humana Press, New Jersey. Pp. 275; indexed; illustrated. Price £99.50.

This book is unlikely to be of interest to the majority of practising anaesthetists. However, for those actively engaged in laboratory research the protocols described might be useful and for some essential.

For example, the pathophysiology of sepsis and its interrelated cytokine networks is currently being dissected in many laboratories. With recent advances in technique, many of which are described in this book, we are now beginning to unravel events at the intracellular level. It may be that this different perspective will simplify a complex and often confusing field. The *Methods in Molecular Biology* series aims to present a collection of linked, easy to follow protocols that can be used at the bench. This particular volume (83) examines in some depth an array of methodologies that examine ligand–receptor and receptor–effector interactions, particularly as they relate to G protein coupled receptors. Many techniques are described, some of which will be familiar to scientists from other disciplines. They include protocols for the preparation of primary antibodies; immunohistochemistry; northern analysis; *in situ* hybridization; methods of altering specific residues in receptor subunits to examine the effect on ligand interaction; and ways of expressing different receptor subunits in various cell systems. More specific protocols that describe the preparation of membrane fragments and measurement of radioligand binding, functional assays of guanine nucleotide exchange at G proteins after agonist binding and techniques to identify and quantitate particular G proteins involved in signalling events are also included. The description of technique and methodology in the majority of cases is detailed and written clearly. Helpful notes are given at the end of each section; usually these are items that you need to know and learn only by experience.

Clearly this is not a book to be read from cover to cover. It is a manual of relevant techniques that will sit comfortably on the top shelf of a laboratory cupboard, in easy reach when inspiration and guidance are required.

J. Slavin

Essentials of Pediatric Intensive Care, 2nd Edn. D. L. Levin and F. C. Morriss (editors). Published by Churchill Livingstone, London. Pp. 1813; indexed; illustrated. Price £48.00.

Paediatric intensive care in the British Isles is undergoing considerable change: the National Health Service has developed a strategy for the future; the Intercollegiate Committee formed by the Royal Colleges of Anaesthesia, Paediatrics and Child Health, and Surgeons has been entrusted with the task of establishing, shaping and approving postgraduate training; specialist status is recognized by the General Medical Council; and trainees are setting their sights on a long-term career in the field. The timing is perfect for a good textbook on paediatric intensive care.

Over the past 10 yr several North American textbooks have defined the domain of expertise and the core knowledge required to practise paediatric intensive care effectively. However, such are the developments in the specialty and general hospital care that one can extrapolate a "critical care" aspect to almost any acute problem requiring admission to hospital. Consequently, rather than becoming more concise, textbooks on the subject have generally increased in size. *Essentials of Pediatric Intensive Care* is no exception. Nevertheless, Levin and Morriss have undertaken and achieved a phenomenal task.

Essentials of Pediatric Intensive Care has the reputation of being a very practical guide. The second edition will not disappoint the reader: 252 contributors with almost every aspect of clinical paediatric intensive care discussed. There is even a chapter written by parents giving their special perspective. The first volume is devoted to pathophysiology, monitoring and treatment, and the second to procedures, equipment and techniques. Nurse and medical practitioners will find that despite its size this is the type of textbook that is helpful and instructive at the bedside. Summary boxes, illustrations and algorithms serve as useful guides and quick references—sadly, the supplementary pocket guide with all of these incorporated, a feature of the first edition, is not supplied with the latest edition. For those such as myself with a predominantly metropolitan practice, the chapters on "shark attack" and "snake envenomations" are a fascinating read. My only criticism is that the reproduction of the radiology examples is generally poor and in some instances woefully inadequate. The only omissions that I could find were: (1) discussion of tracheal tube fixation methods commonly used in the UK and the rest of Europe; (2) a chapter on non-invasive mechanical ventilation; and (3) a chapter on how to set-up a teaching and training programme with suggested requirements for attaining specialist status.

My overall conclusion is that this new edition of *Essentials of Pediatric Intensive Care* remains a very practical textbook and has improved with the expansion to two volumes: a thumbs-up, must-buy, will-use type of book. I recommend it for personal use, but would also suggest that each paediatric intensive care unit has it as part of their library. The only disadvantage for me is that its size implies that I am unlikely to have it with me as a reference when I need it—surely publishers should be moving towards an electronic age with CD versions! Dare I ask, "Is there a web-site yet?"

R. C. Tasker

Manual of Acute Pain Management in Children. I. McKenzie, P. B. Gaukroger, P. Ragg and T. C. K. (Kester) Brown (editors). Published by Churchill Livingstone, Edinburgh. Pp. 224; indexed, illustrated. Price £25.00.

Anyone *au fait* with paediatric anaesthesia will instantly recognize most of the editors of this manual, although why (Kester) Brown has to be named specifically is a mystery. Surely it would be too much of a coincidence to have two paediatric anaesthetists with the initials "T. C. K.", both with the same surname? Nevertheless, this minor irritation does not detract from a worthwhile project.

This manual has 14 contributors from the principal paediatric Australian units, most of whom are anaesthetists with some input from paediatricians, neonatologists and a nurse. The foreword is written by Flank Shann, an intensivist, thus widening further the range of available expertise. However, the reader should not be discouraged by Dr Shann's assertion that this book has been written for "ward medical, surgical and paramedical staff" as there is much that even the most experienced of specialist anaesthetists will find of value. However, academic high-fliers should turn to some other source if they wish to be bogged down by the minutiae of the science of paediatric pain and its treatment, as this is very much a practical manual designed for those working at the coal face of paediatric pain.

The chapters predictably consist of the various techniques available for providing pain relief, for example minor analgesics, nitrous oxide, opioids, PCA, extradural analgesia and peripheral nerve blocks. There are techniques described for providing analgesia in specific situations, such as burns, oncology for neonates, ICU, accident and emergency, and rheumatology, all of which provide good practical advice. However, the strongest selling points are the many algorithms and protocols which are present in great detail throughout the different chapters and in a series of appendices. These are of value not only to physicians organizing a paediatric pain team from the start but also to those with established pain teams. Indeed there is much to interest your reviewer and his colleagues, despite any reputation, deserved or otherwise, which our unit may enjoy.

What are the criticisms? There are a few. The main one concerns the physical make up of the manual which, as an approximately A3 sized paperback, is not easily transported or sturdy, and is more suitable as a bench book rather than an easily accessible manual. The order of the chapters could be set out more logically. It would have been neater to have pain assessment and safety and monitoring before the techniques of pain relief rather than after. A chapter dedicated to pharmacology would have been useful as would highlighted learning points, a device used by many modern textbooks. It may be that the editors have tried to be too brief at the expense of some detail and a list of recommended further reading after each chapter would have been worthwhile.

This is a textbook which will undoubtedly adorn the library shelves of hospital libraries throughout the land. It is to be hoped that it will also be taken down, read, and some of the excellent advice throughout its pages used to provide a framework for setting up and providing pain relief for the children in our care.

L. R. (Roddie) McNicol

Anesthesia and Resuscitation. R. D. M. Jones and R. B. Holland (editors). Published by Butterworth–Heineman, Oxford. Indexed; illustrated.

This book is intended for newly qualified doctors, to "bridge the gap" between academic knowledge and clinical responsibility that all medical graduates must undertake on becoming a house officer. It consists of 38 chapters written by 16 contributors, the majority of whom practice in Australia.

The book is divided into four sections with the majority of chapters written in a short notes/bulleted list style to maintain brevity and clarity. The first section consists of 19 short chapters which cover basic principles of anaesthesia and include pre- and postoperative care, monitoring, general and regional anaesthesia. They are concise but well written and would be ideal introductory texts to new anaesthetists.

The next two sections are in a similar style and cover resuscitation and care of the critically ill patient. Again, they are succinct and easily readable. One chapter is dedicated to crisis management algorithms which have recently been published in anaesthesia journals.

The fourth section covers emergency care of recreational injuries, including hyper- and hypothermia, altitude sickness and decompression injuries. There is also an interesting chapter on management of envenomation by various species indigenous to Australia.

The appendices cover nearly 100 pages and have useful sections on "how to be a streetwise houseofficer", writing examination answers and a compendium of drugs, some of which are not applicable to UK practice. There is also a comprehensive operating theatre discussion guide for undergraduates which would be extremely useful for anaesthetists who teach students.

Personally I liked the style of this book, however I feel it is probably too advanced as "a houseman's guide," although this may reflect the differences in UK and Australian training. For a small textbook it covers a huge range of topics and would probably serve as a useful introductory text for someone considering a career in anaesthesia.

A. Ogilvy

Cardiac Anaesthesia: A Practical Handbook. N. C. Hwang and M. Sinclair. Published by Oxford University Press, Oxford. Pp. 160; indexed; illustrated. Price £45.00.

This handbook is divided into 23 chapters comprising three sections: anatomy, physiology and pharmacology; anaesthesia for adults; and anaesthesia for children. The opening chapters on anatomy, physiology and pharmacology are excellent and give a concise, but clear background to the subsequent clinical sections. Addressing "drugs used in cardiac anaesthesia", thumbnail sketches of anaesthetic, cardiovascular and anticoagulant drugs are outlined. Other drugs described under "organ protection" make up the mixers which complete the cocktail of drugs delivered in cardiac anaesthetic rooms and theatres.

The book is intended for anaesthetic trainees, occasional cardiac anaesthetists and nurses. The clinical sections give unambiguous, straightforward direction, which is frequently unsubstantiated. There is no attempt to be comprehensive in the brief format of the handbook. The techniques reflect UK practice and are appropriate and safe. Emphasis rests on the delivery of anaesthetic care rather than management of likely complications.

Prior knowledge of the text would allow the reader to understand the progress of a cardiac anaesthetic and provide a foundation on which to build clinical experience. The book would be ideal in content and length for a trainee to read before encountering an attachment to cardiac anaesthesia, then re-read at the end of a week to a fortnight in cardiac theatres.

There is some repetition of procedures common to both adults and children in the two clinical sections, which allows either paediatric or adult cardiac anaesthetic practice to be read first. The style of the handbook succeeds better if the sections are read as a narrative. There is not enough space for detail and too brief an index to use the book for reference.

Having read and enjoyed the book from cover to cover at a single sitting the only real disappointment is the ending. The fine introductory chapters lead well into adult cardiac practice. The special requirements of paediatric practice follow, and the book ends with "Early postoperative management". As the index comes into sight on the right hand page, the book ends with the paediatric patient lying in asystole with the chest open. Surely a brief paragraph about the possible improvements in outcome of patients with correctable congenital cardiac anomalies would have sustained better the appreciation of this well paced, enthusiastic and interesting handbook?

D. J. R. Duthie

Anaesthetic Physiology and Pharmacology. W. McCaughey, R. S. J. Clarke, J. P. H. Fee and W. F. M. Wallace (editors). Published by Churchill Livingstone, Edinburgh. Pp. 778; indexed; illustrated. Price £60.00.

This new textbook is a sequel to the well-known *Clinical Anaesthetic Pharmacology*, edited by the late John Dundee. It is a multi-authored text with all the contributors except six emanating from Northern Ireland; although the majority are anaesthetists, the list of contributors also includes distinguished physiologists and obstetricians, and a cell biologist, nephrologist, chemical pathologist and consultant haematologist. The editors' stated intention is to integrate physiology, pharmacology and anaesthesia and they have emphasized those aspects of particular relevance to anaesthesia or critical care.

The quality of the contributors ensures that this text is up to date, accurate and pertinent to clinical practice. However, even with tight editing, the real issue is whether or not it is feasible to cover all the physiological and pharmacological knowledge required of a trainee anaesthetist within a mere 778 pages. For example, chapter one of 10 pages describes chemistry related to anaesthetic practice, and although in a section on "properties on gases and vapours" describes very briefly Boyle's law, solubility, osmotic pressure and ionization, there is no mention of gas viscosity or density. Clinical studies and statistics are covered in a mere 14 pages, albeit well but it is doubtful if comprehension could be obtained from such a short description as opposed to revision of prior knowledge acquired by delving into larger and more discursive texts.

In a seven-page chapter on anaesthetic gases, the space available for describing the effects induced by the blood-gas solubility of nitrous oxide would be inadequate to satisfy the first part of the FRCA examination. Many similar examples could be chosen from throughout this text.

In summary, the editors have attempted the impossible in venturing to encompass within such a circumscribed space the huge knowledge base required in physiology and pharmacology for the anaesthetic trainee. The fact that the end product is so good is a testimony to the quality of the editing and ability of the contributors. I shall certainly use this book frequently in future and shall recommend it to trainees with a caveat that many sections will require supplementation by reading elsewhere in the quest for either comprehension or factual knowledge.

G. Smith

Rapid Sequence Review of Anaesthesiology with Time-limited Pressure. W. K. Chee. Published by Butterworth-Heinemann, Oxford. Pp. 168. Price £27.50.

Professor Chee has written this book for those North American trainees who feel "completely overwhelmed by the amount of information presented in major textbooks", or for those approaching "board examinations" without sufficient time to read larger texts. Although such candidates would be better advised to defer their examinations until more adequately prepared, Professor Chee has attempted to write for them a book whose contents are "concise yet comprehensive . . . and . . . highly concentrated". He also sets an example to us all, in this litigious world, by taking pains to "disclaim any liability caused by direct or indirect application of the information in this book"!

After sitting three international anaesthetic examinations I am in a good position to review this book. I will do so with regard to its usefulness to fellowship candidates who find themselves in either of the above categories. The book attempts to cover most aspects of anaesthesia using headings and lists which might provide frameworks for essays. Commencing with "ABC" and airway problems, then the challenges of pregnancy and paediatrics, chapters proceed to cover trauma, various medical pathologies, anaesthesia for vascular procedures, regional blocks, chronic pain, monitoring and equipment, and some basic pharmacology. Overt omissions include anatomy, ambulatory surgery, infectious diseases/immunosuppression and acute pain relief.

The weakness of a book which has only one contributing author is apparent in the variable standard of information between chapters. Topics which are better covered include obesity, neonatal anaesthesia, and some medical subjects, including cardiovascular and neuromuscular disease. The chapter on respiratory disease contained some useful information, although I was surprised to find that cystic fibrosis, bronchiectasis and bronchopleural fistula did not feature, given their propensity to feature in examinations. One of the hallmarks of the book is its clear, well laid out charts, comparing and contrasting various related pathologies, drugs or equipment. However, I did not like the way in which the resuscitation algorithm (which, incidentally, differed from current European guidelines) was presented as a chart; it should be regarded as a sequence of events, rather than a tick-box which gives lignocaine equal importance to adrenaline in the treatment of ventricular fibrillation.

Inadequate chapters include chapter 20 (pain), a subject of increasing prominence in examinations, which covers only "reflex sympathetic dystrophy" (no "complex regional pain syndromes" here!) and three blocks (stellate ganglion, lumbar sympathetic and coeliac plexus). Backache (the topic of one of my clinical examinations) and the neuralgias are not mentioned. Furthermore, the blocks in both this chapter and chapter19 (regional anaesthesia) are described with little information on techniques and appropriate drug solutions. "Ventilatory modes in ICU" (p. 147) omits BiPAP and HFPPV. "Useful for weaning an intubated patient from the ventilator" is not the first phrase that springs to mind when considering Ayre's T-piece (p. 148). Chapter 9 (trauma) ignores the sequence of primary and secondary surveys, and would have done better to expand on the subjects of facial and thoracic trauma than to merely list them as possible occurrences. Transfusion therapy is also poorly covered.

Obviously 168 pages cannot include everything, particularly when the text is so widely spaced, but this book fell short of the usefulness I found with my own favourite crammer-style textbooks in several respects. First, the amount of information in the book is well below the standard required of the final FRCA (although it may be of some value to part 1 candidates in the clinical part of their examination). Second, the author has not quite appreciated the type of information which fellowship candidates easily forget and upon which they may need prompting in the days immediately preceding the examinations. (Admittedly there is more than adequate room on each page to add one's own notes, but there are cheaper ways of making a notebook.) Third, with its A4 size pages and weighing 580 g, it is too cumbersome a book to be carried around easily and opened when convenient. Fourth, the lack of an index diminishes the user-friendliness of the book. Finally, Professor Chee has managed to neither provoke nor inspire readers to be familiar with the more important well known articles or current controversies (only four references and a bibliography are listed), and to be able to discuss how these relate to one's own practice. It is knowledge such as this which helps to signify to the examiner that one is ready to embark upon the next stage of training.

S. Winship

AUTHOR INDEX

VOLUME 79

British Journal of Anaesthesia

ARS = Anaesthetic Research Society Abstracts

EACTA = European Association of Cardiothoracic Anaesthesiologists Abstracts

C = Correspondence

E = Editorial

R = Book Review

e = Erratum

Abay, G., Çoruh, T., Aykaç, Z., Aydoğan, H., Aykut, S., Eren, E. and Canik, S. Intravenous clonidine administration during CPB: effects on haemodynamic parameters and extubation time, (*EACTA*) A.8

Abdulatif, M. and El-Sanabary, M. Blood flow and mivacurium-induced neuromuscular block at the orbicularis oculi and adductor pollicis muscles 24–28

Absalom, A. R., Pledger, D. R. and Kong, A. Effects of a single dose of etomidate on adreno-cortical function in the critically ill, (*ARS*) 679P

Adams, M. *see* Dresner, M., (*C*) 813

Addy, E. V. *see* Brain, A. I. J. 699–703, 704–709; Kapila, A. 710–713

Akazawa, S. *see* Nakaigawa, Y. 363–368

Akpir, K. *see* Tuğrul, E. 306–310

Albanese, C. *see* Bertolissi, M., (*EACTA*) A.61

Albano, J. D. M. *see* MacLaren, A. J , (*EACTA*) A.17

Albin, M. S., (editor) *Textbook of Neuroanesthesia with Neurosurgical and Neuroscience Perspectives*, (*R*) 412

Albrecht, S. *see* Dingemanse, J. 567–574

Alexander, J. I. Pain after laparoscopy 369–378

Ali, P. *see* Elton, C. D., (*E*) 551–554

Allsop, J. R. Prophylaxis against deep vein thrombosis, (*C*) 145

Al-Rawi, P. *see* Gupta, S., (*ARS*) 680P

Althaus, U. *see* Walpoth, B. H., (*EACTA*) A.30; (*EACTA*) A.37

Ammar, A. *see* Naguib, M. 450–455

Ammar, T., Silvay, G. and Reich, D. L. Platelet effects of aprotinin and tranexamic acid, (*EACTA*) A.68

Andrews, C. J. H. *see* Sneyd, J. R. 427–432

Andrews, P. J. D. *see* Souter, M. J. 97–102

Antkowiak, B., Hentschke, H. and Kirschfeld, K. Effects of volatile anaesthetics on spontaneous action potential firing of cerebellar Purkinje cells *in vitro* do not follow the Meyer–Overton rule 617–624

Antonini, M. *see* Della Rocca, G., (*EACTA*) A.77

Antzaka, Ch. *see* Papadimitriou, L., (*EACTA*) A.51

Aoki, H., Inoue, M., Mizobe, T., Harada, M., Imai, H. and Kobayashi, A. Platelet function is inhibited by nitric oxide liberation during nitroglycerin-induced hypotension anaesthesia 476–481

Aouifi, A., Filley, S., Neidecker, J., Helal, N., Bompard, D., Vedrinne, C., Blanc, P., Laroux, M. C., Bouvier, H., Girard, C. and Lehot, J. J. Methaemoglobin (MetHb) production during nitric oxide (NO) inhalation, (*EACTA*) A.93

Aouifi, A., Vedrinne, C., Neidecker, J., Bompard, D., Cherfa, A., Brulé, P., Gressier, M., Laroux, M. C., Tronc, F., Ninet, J., Champsaur, G. and Lehot, J. J. Arterial switch for transposition of great arteries anaesthesia & postoperative care, (*EACTA*) A.91

AÞkar, F. Z , Çevik, A., Demirað, K., Sakarya, M. and Durmaz, Ý. Evaluation of the effects of diltiazem on myocardial protection with troponin T in coronary artery bypass graft surgery, (*EACTA*) A.28

AÞkar, F. Z. *see* Erhan, E., (*EACTA*) A.56

Appadu, B. L *see* Hirota, K., (*ARS*) 141P

Archer, D. P. and Roth, S. H. Pharmacodynamics of thiopentone: nocifensive reflex threshold changes correlate with hippocampal electroencephalography 744–749

Ariffin, S. *see* Manji, M., (*EACTA*) A.14; (*EACTA*) A.87

Armellin, G. *see* Pittarello, D., (*EACTA*) A.42

Arnstein, F. Catalogue of human error 645–656

Artigas, A. *see* Pinsky, M. R., (*R*) 266

Asada, A. *see* Hase, I. 740–743

Asai, T., Mapleson, W. W. and Power, I. Effects of nalbuphine, pentazocine and U50488H on gastric emptying and gastrointestinal transit in the rat, (*ARS*) 676P; Interactive effects of morphine and dexmedetomidine on gastrointestinal transit and gastric emptying in the rat, (*ARS*) 133P; Naloxone inhibits gastric emptying but not gastrointestinal transit in the rat, (*ARS*) 133P

Asai, T. *see* Koga, K., (*ARS*) 681P

Asbury, A. J. *see* Hawksworth, C. R. E., (*ARS*) 139P

Atar, D. *see* Seeberger, M. D., (*EACTA*) A.40

Atcheson, R., Bjornstrom, K., Hirst, R. A., Rowbotham, D. J. and Lambert, D. G. Effect of halothane on K$^+$ and carbachol stimulated noradrenaline release and increased in SH-SY5Y human neuroblastoma cells 78–83

Atcheson, R. *see* Joyce, P. I., (*ARS*) 677P

Atherton, A. M. J. *see* Mostafa, S. M. 392–393

Auf der Maur, P. *see* Walpoth, B. H., (*EACTA*) A.37

Aupart, M. *see* Lemoine, E., (*EACTA*) A.54

Ausseur, A., Chalons, N., Marquette, C. H., Bello, N. and Scherpereel, P. Cutaneous blood gas monitoring during rigid bronchoscopy with high frequency Jet ventilation (HFJV), (*EACTA*) A.74

Ayala, J. L. and Coe, A. Thermal softening of tracheal tubes: an unrecognized hazard of the Bair Hugger active patient warming system 543–545

Aydoğan, H. *see* Abay, G., (*EACTA*) A.8

Aykaç, Z. *see* Abay, G., (*EACTA*) A.8; Suzer, A., (*EACTA*) A.52; Suzer, Ö., (*EACTA*) A.1; Taç, T., (*EACTA*) A.25

Aykut, S. *see* Abay, G., (*EACTA*) A.8

Babic, M. *see* Jovic, M., (*EACTA*) A.35

Baines, P. *see* Whitehead, C. F., (*C*) 813–814

Bakola, A. A., Skubas, N. J , McCawley, C., Lappas, D. G. and Cox, J. L. Echocardiographic and haemodynamic differences among patients undergoing the MAZE procedure, (*EACTA*) A.44

Ballesteros, M., Welters, I., Boldt, J., Zickmann, B., Knothe, C. and Hempelmann, G. Effect of intravascular volume load after induction of anaesthesia on oxygen consumption in cardiac surgery patients, (*EACTA*) A.19

Balogh, D., Mair, P., Hormann, Ch., Mair, J., Margreiter, J., Muller, L. and Puschendorf, B. Crystalloid vs. blood cardioplegia: a comparison of myocardial markers, (*EACTA*) A.26

Bamigbade, T. A., Davidson, C., Langford, R. M. and Stamford, J. A. Actions of tramadol, its enantiomers and principal metabolite, O-desmethyltramadol, on serotonin (5-HT) efflux and uptake in the rat dorsal raphe nucleus 352–356

Banas, S. *see* Knapik, P., (*EACTA*) A.94

Bapat, P. and Verghese, C. Cuff deflation for easier weaning from ventilation, (*C*) 145

Bapat, P. P. and Verghese, C. Weaning: is the work of breathing via a tracheostomy tube similar to that via a tracheal tube? (*C*) 815

Barankay, A., Holper, K., Haehnel, J. C., Braun, S., Richter, J. A. and Meisner, H. Cardiac troponin I release

using different myocardial management strategies, (*EACTA*) A.27
Barrière, J C. *see* Lemoine, E., (*EACTA*) A.54
Barson, J. *see* Plowman, A., (*C*) 143–144
Barthel, H. *see* Schlack, W. 88–96
Bartunek, A., Pernerstorfer, T., Parschalk, P. and Wenisch, C., Hiesmayr, M. Antibiotic prophylaxis with cefodizime in patients with CABG-operations, (*EACTA*) A.62
Baskett, P. J. F. and Strunin, L. Resuscitation, (*E*) 149–150
Baskett, P. J. F. *see* Gabbott, D. A. 159–171
Basler, M. *see* Makin, A., (*ARS*) 687P
Bassi, A. *see* Borghi, B. 662–664
Bassi, F. *see* Bertolissi, M., (*EACTA*) A.60; (*EACTA*) A.61
Baumgartner, I *see* Walpoth, B. H., (*EACTA*) A.37
Baumgartner, R. *see* Walpoth, B. H., (*EACTA*) A.37
Bazin, J. E. and Schoeffler, P. Pigs are not humans, (*C*) 691
Beatty, P. C. W. Preliminary survey into clinical attitudes to computer based decision support systems, (*ARS*) 140–141P
Been, H. D. *see* Ubags, L. H. 590–594
Bellam, M. C. *see* Davey-Quinn, A., (*ARS*) 684–685P
Bellamy, M. C., Galley, H. F. and Webster, N. R. Changes in inflammatory mediators during orthotopic liver transplantation 338–341
Bellamy, M C. *see* O'Beirne, H. A., (*ARS*) 132P; Srinivasa, R., (*ARS*) 686P
Bello, N. *see* Ausseur, A., (*EACTA*) A.74
Ben-David, B. and Stahl, S. Prognosis of intraoperative brachial plexus injury: a review of 22 cases 440–445
Bendixen, D. *see* Quane, K. A. 332–337
Bendyk, K. *see* Buhre, W., (*EACTA*) A.4
Bengtsson, M., Nettelblad, H. and Sjoberg, F. Extradural catheter-related infections in patients with infected cutaneous wounds 668–670
Benhamou, D. *see* Lentschener, C., (*C*) 691–692
Bennett, S. R., McKeown, A. J. P. and Griffin, S. C. Effects of antiotensin on renal function in cardiac surgical patients, (*EACTA*) A.18; Haemodynamic response to angiotensin in patients treated with angiotensin converting enzyme inhibitors, (*EACTA*) A.13
Ben-Shlomo, I. *see* Tverskoy, M. 798–800
Berg, K. *see* Quane, K. A. 332–337
Bergfeld, L. *see* Runsio, M., (*EACTA*) A.20
Bernabei, R. *see* Zuccala, G 776–781
Bertolissi, M., Bassi, F., Da Broi, U. and De Monte, A. Transport and surgical ischaemic times: Can they have a different influence on the cardiovascular function after orthotopic heart transplantation? (*EACTA*) A.60
Bertolissi, M., Di Bartolomeo, S., Albanese, C. and Bassi, F. Impact of preoperative pulmonary vascular resistance and ischaemic time on the cardiovascular function after orthotopic heart transplantation, (*EACTA*) A.61
Bito, H. *see* Katoh, T. 465–468; Moriwaki, G. 782–786
Bittner, R. E. *see* Mader, N. 125–127
Bjorkman, S., Rigemar, G. and Idvall, J. Pharmacokinetics of midazolam given as an intranasal spray to adult surgical patients 575–580
Bjornstrom, K. *see* Atcheson, R. 78–83
Blackl, A *see* Caleb, P., (*ARS*) 682P
Blaicher, A. *see* Hartmann, T. 482–487
Blaise, G. *see* Troncy, E. 631–640
Blanc, P. *see* Aouifi, A., (*EACTA*) A.93
Bloomfield, S. *see* Morton, C. P. J. 3–8
Boen, P. *see* Sneyd, J. R. 433–439
Bojic, M. *see* Jovic, M., (*EACTA*) A.35; Vuk, Lj., (*EACTA*) A.96
Boldt, J., Papsdorf, D., Uphus, D., Muller, M. and Hempelmann, G. Changes in regulators of the circulation in patients undergoing lung surgery 733–739
Boldt, J. *see* Ballesteros, M., (*EACTA*) A.19; Welters, I., (*EACTA*) A.22
Bolsin, S. *see* Plowman, A., (*C*) 143–144
Bolton, P. *see* Makin, A., (*ARS*) 687P
Bombardini, T. *see* Borghi, B. 662–664
Bompard, D. *see* Aouifi, A., (*EACTA*) A.91; (*EACTA*) A.93
Bonnet, F. *see* Gentili, M. 660–661
Booij, L. H. D. J. *see* Vermeulen, P. M. 488–496
Booker, P. D., Davis, A. J. M. and Franks, R. Gut mucosal perfusion in infants undergoing cardiopulmonary bypass: effect of preoperative captopril 14–18
Booker, P. D. *see* Cheung, S. L. W. 9–13; Prosser, D. P. 293–296
Borgeat, A. and Kwiatkowski, D. Spontaneous movements associated with rocuronium: is pain on injection the cause? 382–383
Borghi, B., Pignotti, E., Montebugnoli, M., Bassi, A., Corbascio, M., de Simone, N., Elmar, K., Righi, U., Laguardia, A. M., Bugamelli, S., Cataldi, F., Ranocchi, R., Feoli, M. A., Bombardini, T., Gargioni, G., Franchini, A. G. and Caroli, G. C. Autotransfusion in major orthopaedic surgery: experience with 1785 patients 662–664
Borm, G. F. *see* Vermeulen, P. M. 488–496
Bornscheuer, A. *see* Leuwer, M., (*ARS*) 132P
Bortolotti, U. *see* Ruschi, S., (*EACTA*) A.67
Bossaert, L. L. Fibrillation and defibrillation of the heart 203–213
Bossard, A. E. *see* Camus, Y. 796–797
Bosson, J.-L. *see* Mezin, P. 327–331
Botanto, R. *see* Pittarello, D., (*EACTA*) A.42
Bòttiger, R. H., Motsch, B. W., Muller, J., Fleischer, F. and Martin, E. Pulse contour cardiac output measurement corresponds better with standard dilution technique than continuous thermodilution technique after hypothermic bypass, (*EACTA*) A.32
Boudard, C. *see* Gressier, M., (*EACTA*) A.78
Boutel, D. *see* Lagonidis, D., (*EACTA*) A.46
Bouvier, H. *see* Aouifi, A., (*EACTA*) A.93
Bowey, C. J. *see* Fisher, M. McD 59–63
Boyett, M. R. *see* Davies, L. A., (*ARS*) 135P
Brain, A. I. J., Verghese, C., Addy, E. V. and Kapila, A. The intubating laryngeal mask. I: development of a new device for intubation of the trachea 699–703
Brain, A. I. J., Verghese, C., Addy, E. V., Kapila, A. and Brimacombe, J. The intubating laryngeal mask. II: a preliminary clinical report of a new means of intubating the trachea 704–709
Brain, A. I. J. *see* Kapila, A. 710–713
Brambilla, E. *see* Mezin, P. 327–331
Braun, S. *see* Barankay, A., (*EACTA*) A.27
Brennan, L. *see* Griffin, M. J., (*ARS*) 138P
Brennum, J. *see* Ilkjær, S. 600–605
Brett, W *see* Seeberger, M. D., (*EACTA*) A.40
Brimacombe, J. *see* Brain, A. I. J. 704–709
Brimioulle, S. *see* Ewalenko, P. 625–630
Broka, S. *see* Collard, E., (*EACTA*) A.65; (*EACTA*) A.86
Brown, T. C. K. (Kester) *see* McKenzie, I., (*R*) 819
Brulé, P. *see* Aouifi, A., (*EACTA*) A.91
Brune, J. *see* Gressier, M., (*EACTA*) A.78
Brunner, M. D. *see* Sharpe, R. M., (*C*) 410–411
Brunner, M. D. *see* Shinner, G., (*ARS*) 137–138P
Bryant, D. J. *see* Lockwood, G. G. 581–585; 586–589
Buche, M. *see* Collard, E., (*EACTA*) A.86
Bugamelli, S. *see* Borghi, B. 662–664
Buhre, W., Hoeft, A., Schorn, B., Weyland, A., Scholz, M. and Sonntag, H. Acute effect of mitral valve replacement on extravascular lung water in patients receiving colloid or crystalloid priming of cardiopulmonary bypass 311–316
Buhre, W., Schmidt, M., Bendyk, K., Kazmaier, S., Spiegel, T.v., Weyland, A. and Sonntag, H. Effects of fentanyl-midazolam anaesthesia on intrathoracic and total blood volume, (*EACTA*) A.4
Buhre, W. *see* Giannaris, S., (*EACTA*) A.23; Kazmaier, S., (*EACTA*) A.33; (*EACTA*) A.88; Mielck, F., (*EACTA*) A.6; Spiegel, T.v., (*EACTA*) A.3; Weyland, A., (*EACTA*) A.53; Wietasch, G., (*EACTA*) A.59
Buket, S. *see* Erhan, E., (*EACTA*) A.56
Burden, R. J. and McQuillan, P. J. Converting pH and H^+: a "rule of thumb", (*e*) 413
Burm, A. G. L. *see* Veering, B. Th., (*C*) 144–145
Bursch, J *see* Wietasch, G., (*EACTA*) A.59
Butt, M. W. *see* Raphael, J. H. 473–475
Byrne, A. J. and Gareth Jones, J. The expanding role of simulators in risk management, (*C*) 411
Byrne, A. J. and Jones, J G. Simulated anaesthetic emergencies, (*C*) 690–691

Cafferkey, M. *see* Paris, S. T. 280–284
Caillet, J. B. *see* Gressier, M., (*EACTA*) A.78
Caleb, P., Sharpe, P. K., Blackl, A. and Day, C. Artificial neural networks for distinguishing disturbed from undisturbed breathing, (*ARS*) 682P
Callingham, B. C. *see* Vuylsteke, A., (*EACTA*) A.11
Calvey, T. N. and Williams, N. E. *Principles and Practice of Pharmacology for Anaesthetists*, 3rd Edn, (*R*) 549
Camci, E. *see* Tuğrul, E. 306–310
Çamcý, E., Tuŏrul, M., Gençelli, J., Yavru, A. and Pembeci, K. Comparison of propofol and isoflurane ameliorating effects during rewarming period in paediatric cardiac surgery, (*EACTA*) A.58
Campbell, W. I. and Kendrick, R. W. Pre-emptive analgesia using local anaesthesia: a study in bilaterally symmetrical surgery 657–659
Camu, F. *see* Verborgh, C., (*EACTA*) A.10

Camus, Y., Delva, E., Bossard, A. E., Chandon, M. and Lienhart, A. Prevention of hypothermia by cutaneous warming with new electric blankets during abdominal surgery 796–797

Candiani, A. *see* Latronico, N., (*C*) 547–548

Canik, S. *see* Abay, G., (*EACTA*) A.8

Caroli, G. C. *see* Borghi, B. 662–664

Carrel, T. *see* Walpoth, B. H., (*EACTA*) A.30

Carroll, M. *see* McCourt, K. C., (*ARS*) 134P

Carroll, M. T., Lowry, D., Mirakhur, R. K. and McCourt, K. C. Comparison of neuromuscular blocking effects and train-of-four fade of cisatracurium with other blocking agents, (*ARS*) 683P

Carson, D. *see* Makin, A., (*ARS*) 687P

Cataldi, F. *see* Borghi, B. 662–664

Caviezel, F. *see* Ranucci, M., (*EACTA*) A.84

Cavill, G. *see* Girling, K. J., (*ARS*) 131P; Wrench, I. J. 541–542

Cazzaniga, A. *see* Ranucci, M., (*EACTA*) A.84; (*EACTA*) A.85

Celik, B. *see* Walpoth, B. H., (*EACTA*) A.30

Çevik, A. *see* Apkar, F. Z., (*EACTA*) A.28

Chakrabarti, M. K. *see* Ma, D., (*ARS*) 141–142P; 525–529; (*ARS*) 686–687P

Challis, R. A. J., (editor) *Methods in Molecular Biology, volume 83: Receptor Signal Transduction Protocols*, (*R*) 818

Chalons, N. *see* Ausseur, A., (*EACTA*) A.74

Chamberlain, D. Peri-arrest arrhythmias 198–202

Champsaur, G. *see* Aouifi, A., (*EACTA*) A.91

Chan, H.-L. *see* Huang, H.-H. 754–758

Chandon, M. *see* Camus, Y. 796–797

Charbonneau, M. *see* Troncy, E. 631–640

Charters, P. *see* Groom, P., (*ARS*) 135P; (*ARS*) 680–681P; Hawkins, M., (*ARS*) 136–137P; Molnar, Z., (*ARS*) 679–680P

Chassard, D. *see* Tournadre, J.-P. 514–516

Chee, W. K. *Rapid Sequence Review of Anaesthesiology with Time-limited Pressure*, (*R*) 820

Cherfa, A. *see* Aouifi, A., (*EACTA*) A.91

Cheung, S. L. W., Booker, P. D., Franks, R. and Pozzi, M. Serum concentrations of bupivacaine during prolonged continuous paravertebral infusion in young infants 9–13

Chhibber, A. K. *see* Nguyen, T. T. 801–803

Chong, Z.-K., Jawan, B., Poon, Y.-Y. and Lee, J.-H. Unsuspected difficult intubation caused by a laryngeal web 396–397

Christiansen, C. L., Jakobsen, C.-J. and Noreng, M. Hepatic venous blood flow measured with retrograde thermodilution technique, (*EACTA*) A.55

Cirri, S. *see* Ranucci, M., (*EACTA*) A.84; (*EACTA*) A.85

Cittadini, A. *see* Zuccala, G. 776–781

Civetta, J. M., Taylor, R. W. and Kirby, R. R., (editors) *Critical Care*, 3rd Edn, (*R*) 265

Civetta, J. M. *see* Kirby, R. R., (*R*) 147

Clarke, J. *see* Plowman, A., (*C*) 143–144

Clarke, R. S. J. *see* McCaughey, W., (*R*) 820

Clyti, N. *see* Diemunsch, P. 322–326

Cocchi, A. *see* Zuccala, G. 776–781

Coccia, C. *see* Della Rocca, G., (*EACTA*) A.77

Coe, A. *see* Ayala, J. L. 543–545

Collard, E., Ducart, A., Buche, M., Broka, S., Gonzalez, M., Jamart, J. and Joucken, K. Postoperative morbidity after coronary artery bypass graft surgery without cardiopulmonary bypass, (*EACTA*) A.86

Collard, E., Ducart, A., Dursin, A., Dsselaer, J. C., Broka, S., Jamart, J. and Joucken, K. Effects of preoperative i.v. heparin in coronary artery bypass grafting, (*EACTA*) A.65

Collins, L. M., Cooney, C. M. and Fitzpatrick, G. Propofol induction characteristics after fentanyl or midazolam and fentanyl, (*ARS*) 676–677P

Comite, C. *see* Ruschi, S., (*EACTA*) A.67

Comunale, M. E. *see* Kussman, B. 122–124

Conacher, I. D. Anaesthesia for the surgery of emphysema 530–538

Conacher, I. D. *see* McMahon, C. C., (*EACTA*) A.75

Conseiller, C. *see* Diemunsch, P. 322–326

Conti, D. *see* Ranucci, M., (*EACTA*) A.85

Conzen, P. *see* Szekely, A., (*EACTA*) A.15

Cooney, C. M. *see* Collins, L. M., (*ARS*) 676–677P

Corbascio, M. *see* Borghi, B. 662–664

Cordier, J. F. *see* Gressier, M., (*EACTA*) A.78

Çoruh, T. *see* Abay, G., (*EACTA*) A.8; Taş, T., (*EACTA*) A.25

Coursin, D. *see* Murray, M., (*R*) 267

Couto da Silva, J. M., Mapleson, W. W. and Vickers, M. D. Quantitative study of Lowe's square-root-of-time method of closed-system anaesthesia 103–112

Cox, J. L. *see* Bakola, A. A., (*EACTA*) A.44

Cross, M. *see* Sneyd, J. R. 427–432; 433–439

Cross, M. H. *see* O'Connor, P. J., (*EACTA*) A.31

Crossley, A. W. A. *see* Wrench, I. J. 541–542

Cunningham, A. J. *see* McKeague, H., (*E*) 415–416

Curran, J. L., Hall, W. J., Halsall, P. J., Hopkins, P. M., Iles, D. E., Markham, A. F., Robinson, R. L., West, S. P. and Ellis, F. R. Genetic analysis reveals single recombinants in malignant hyperthermia, (*ARS*) 134P

Cuthbertson, B. H., Stott, S. and Webster, N. R. Use of inhaled nitric oxide in the critically ill, (*C*) 814

Da Broi, U. *see* Bertolissi, M., (*EACTA*) A.60

Dahl, J. B. *see* Ilkjær, S. 600–605

Dale, H. *see* Sneyd, J. R. 433–439

Daniell, C. J. *see* Sneyd, J. R. 427–432

Daunderer, M. *see* Schwender, D. 53–58

Davey-Quinn, A. and Bellam, M. C. Functional iron deficiency in orthotopic liver transplantation, (*ARS*) 684–685P

Davidson, C. *see* Bamigbade, T. A. 352–356

Davies, L. A., Harrison, S. M., Boyett, M. R. and Hopkins, P. M. Dose-dependent effects of halothane on contraction of rat ventricular myocytes, (*ARS*) 135P

Davis, A. *see* Prosser, D. P. 293–296

Davis, A. J. M. *see* Booker, P. D. 14–18

Day, C. *see* Caleb, P., (*ARS*) 682P

Deacock, S. and Holdcroft, A. Heat retention using passive systems during anaesthesia: comparison of two plastic wraps, one with reflective properties 766–769

Decoene, C., Jude, B., Prat, A., Dupond, J. and Shaaban, M. Analysis of fibrinolysis during coronary artery surgery, (*EACTA*) A.66

De Lange, S. *see* Langenberg, C. J. M., (*EACTA*) A.50

de Lasson, L., Hansen, H. E., Juhl, B., Paaske, W. P. and Pedersen, E. B. Effect of felodipine on renal function and vasoactive hormones in infrarenal aortic surgery 719–725

Delcroix, M. *see* Ewalenko, P. 625–630

Deligianni, M. *see* Nicolaides, A., (*EACTA*) A.45; Papadimitriou, L., (*EACTA*) A.51

Della Rocca, G., Coccia, C., Pugliese, F., Antonini, M., Pompei, L., Maritti, M. and Ruberto, F. Inhaled nitric oxide during anaesthesia for lung transplant, (*EACTA*) A.77

Delva, E. *see* Camus, Y. 796–797

Demirağ, K. *see* Apkar, F. Z., (*EACTA*) A.28

De Monte, A. *see* Bertolissi, M., (*EACTA*) A.60

De Perrot, M. *see* Vassalli, F., (*EACTA*) A.79

Dergeloo, O. *see* Seeberger, M. D., (*EACTA*) A.40

De Roover, E. *see* Verborgh, C., (*EACTA*) A.10

Desai, J. *see* Mills, G. H. 726–732

De Schryver, D. *see* Foubert, L., (*EACTA*) A.90

de Simone, N. *see* Borghi, B. 662–664

De Sole, P. *see* Zuccala, G. 776–781

Deusch, E. *see* Germann, R. 357–362

Devi, L. A. *see* Hirota, K., (*ARS*) 141P

Devitt, J. H. *see* Kurrek, M., (*C*) 689

Dewan, D. M. and Hood, D. D., (editors) *Practical Obstetric Anesthesia*, (*R*) 147

Dexter, F. and Hindman, B. J. Effect of haemoglobin concentration on brain oxygenation in focal stoke: a mathematical modelling study 346–351

D'haese, J. *see* Verborgh, C., (*EACTA*) A.10

Dhainaut, J.-F. *see* Pinsky, M. R., (*R*) 266

Di Bartolomeo, S. *see* Bertolissi, M., (*EACTA*) A.61

Dick, W. F. Uniform reporting in resuscitation 241–252

Dickson, M. A. S., Moores, C. and McClure, J. H. Comparison of single, end-holed and multi-orifice extradural catheters when used for continuous infusion of local anaesthetic during labour 297–300

Diemunsch, P., Conseiller, C., Clyti, N., Mamet, J. P. and French Ondansetron Study Group Ondansetron compared with metoclopramide in the treatment of established postoperative nausea and vomiting 322–326

Dillon, P. J. *see* Nguyen, T. T. 801–803

Dimitriou, S. *see* Nicolaides, A., (*EACTA*) A.45

Dimitriou, St. *see* Papadimitriou, L., (*EACTA*) A.51

Dingemanse, J., Häussler, J., Hering, W., Ihmsen, H., Albrecht, S., Zell, M., Schwilden, H. and Schüttler, J. Pharmacokinetic–pharmacodynamic modelling of the EEG effects of Ro 48-6791, a new short-acting benzodiazepine, in young and elderly subjects 567–574

Diri, E. *see* Suzer, Ö., (*EACTA*) A.1

Dirks, J. *see* Ilkjær, S. 600–605

Dirksen, R. *see* Vermeulen, P. M. 488–496

Dob, D. P. *see* Lockwood, G. G. 581–585; 586–589

Doenicke, A., Roizen, M. F., Hoernecke, R., Mayer, M., Ostwald, P. and Foss, J. Haemolysis after etomidate:

comparison of propylene glycol and lipid formulations 386–388

Doré, C. J. *see* Sharpe, R. M., (*C*) 410–411

Doré, C. J. *see* Shinner, G., (*ARS*) 137–138P

Doyle, E. and Goggin, P. *MCQs and OSCEs for the Primary FRCA*, (*R*) 818

Dresner, M., Adams, M. and Klein, H. Ropivacaine test dose in extradural anaesthesia, (*C*) 813

Drummond, G. B. *see* Foo, I. T. 41–46

Drummond, J. C. *see* Ubags, L. H. 590–594

Ducart, A. *see* Collard, E., (*EACTA*) A.65; (*EACTA*) A.86

Dupond, J. *see* Decoene, C., (*EACTA*) A.66

Dupont, A. *see* Verborgh, C., (*EACTA*) A.10

Durmaz, Y. *see* Aþkar, F. Z., (*EACTA*) A.28

Dursin, A. *see* Collard, E., (*EACTA*) A.65

Durward, A. *see* Hatherill, M. 665–667

Eadie, R. *see* Ramasamy, D. 394–395

Eckersall, S *see* Elliott, S. 446–449

Edmondson, L. Intraocular pressure and suxamethonium, (*C*) 146

Eger, E. I. *see* Griffiths, R. 389–391

El-Kabsh, M. Y. *see* Kotb, H. I. M. 804–806

Elliott, S., Eckersall, S., Fligelstone, L. and Jothilingam, S. Does the addition of clonidine affect duration of analgesia of bupivacaine wound infiltration in inguinal hernia surgery? 446–449

Ellis, F. R. *see* Curran, J. L., (*ARS*) 134P; Enright, S. M., (*ARS*) 685P

Ellis, F. R. *see* Hopkins, P. M., (*R*) 266

Elmar, K. *see* Borghi, B. 662–664

El-Sanabary, M. *see* Abdulatif, M. 24–28

Elton, C. D., Ali, P. and Mushambi, M. C. "Walking extradurals" in labour: a step forward? (*E*) 551–554

Emara, S. E. S. *see* Kotb, H. I. M. 804–806

Engelmann, E. *see* Rauch, H., (*EACTA*) A.2

Enright, S. M., Ellis, F. R., Halsall, P. J. and Hopkins, P. M. Is there a difference in myofilament calcium sensitivity between malignant hyperthermia susceptible and normal skeletal muscle? (*ARS*) 685P

Enright, S M. *see* Srinivasa, R., (*ARS*) 686P

Enrini, R. *see* Ranucci, M., (*EACTA*) A.84

Erdogan, O. *see* Süzer, Ö., (*EACTA*) A.1

Eren, E. *see* Abay, G., (*EACTA*) A.8

Erhan, E., Aþkar, F. Z., Büket, S., Özbaran, M., Gunel, Ö. and Erhan, Y. Effects of ventilation during cardiopulmonary bypass on pulmonary shunt, compliance and structure, (*EACTA*) A.56

Erhan, Y. *see* Erhan, E., (*EACTA*) A.56

Evans, R. *see* Piriou, V. 68–77

Ewalenko, P., Brimioulle, S., Delcroix, M., Lejeune, P. and Naeije, R. Comparison of the effects of isoflurane with those of propofol on pulmonary vascular impedance in experimental embolic pulmonary hypertension 625–630

Fagerlund, T. *see* Quane, K. A. 332–337

Fallegger, B. *see* Walpoth, B. H., (*EACTA*) A.37

Fang, Z. *see* Griffiths, R. 389–391

Faroqui, M. *see* Manji, M., (*EACTA*) A.14; (*EACTA*) A.87

Fassoulaki, A. MAC values of mixtures, (*C*) 410

Fee, J. P. H. *see* McCaughey, W., (*R*) 820

Feihl, F. *see* Perret, C., (*R*) 266

Feneck, R. O. *see* Tupper-Carey, D. A., (*EACTA*) A.29; (*EACTA*) A.36

Feoli, M. A. *see* Borghi, B. 662–664

Filley, S. *see* Aouifi, A., (*EACTA*) A.93

Finsterer, U. *see* Schwender, D. 53–58

Firmin, R. K. *see* Peek, G. J., (*C*) 260

Fischer, F. *see* Isetta, C., (*EACTA*) A.69

Fisher, M. McD and Bowey, C. J. Intradermal compared with prick testing in the diagnosis of anaesthetic allergy 59–63

Fitzgerald, M *see* Marsh, D. F. 787–795

Fitzpatrick, G *see* Collins, L. M., (*ARS*) 676–677P

Flameng, W. *see* Raez, R., (*EACTA*) A.47

Fleischer, F. *see* Bottiger, R. H., (*EACTA*) A.32

Fleyshman, G. *see* Tverskoy, M. 798–800

Fligelstone, L. *see* Elliott, S. 446–449

Flynn, P. J. *see* Paris, S. T. 280–284

Foex, P. *see* Piriou, V. 68–77

Foo, I. T., Warren, P. M. and Drummond, G. B. Effect of domperidone on the ventilatory response to transient hyperoxia in patients anaesthetized with isoflurane 41–46

Forsyth, A. *see* Mills, G. H. 726–732

Foss, J. *see* Doenicke, A. 386–388

Fouad, E. A. *see* Kotb, H. I. M. 804–806

Foubert, L., Mareels, K., Rijckaert, D., De Schryver, D., Rolly, G. and Van Nooten, G. Haemodynamic effects of celiprolol and sotalol after coronary artery bypass grafting, (*EACTA*) A.90

Franchini, A. G. *see* Borghi, B. 662–664

Francœur, M. *see* Troncy, E. 631–640

Franks, R. *see* Booker, P. D. 14–18; Cheung, S. L. W. 9–13

Frederick, L. A. *see* Nakatsuka, M., (*EACTA*) A.76

Fredman, B., Olsfanger, D. and Jedeikin, R. Thorascopic sympathectomy, (*C*) 688; Thorascopic sympathectomy in the treatment of palmar hyperhidrosis: anaesthetic implications 113–119

Fredman, B. *see* Olsfanger, D. 317–321

French Ondansetron Study Group *see* Diemunsch, P. 322–326

Frohlich, D., Schwall, B., Funk, W. and Hobbhahn, J. Laryngeal mask airway and uncuffed trachael tubes are equally effective for low flow or closed system anaesthesia in children 289–292

Fujii, Y., Toyooka, H. and Tanaka, H. Granisetron reduces the incidence of nausea and vomiting after middle ear surgery 539–540

Fukuda, H. *see* Hirabayashi, Y. 563–566

Funk, W. *see* Frohlich, D. 289–292

Gaba, D. M. and Howard, S. K. Simulated anaesthetic emergencies, (*C*) 689–690

Gabbott, D. A. and Baskett, P. J. F. Management of the airway and ventilation during resuscitation 159–171

Gale, L. B. *see* Young, J. D. 398–401

Galletly, D. C. and Larsen, P. D. Cardioventilatory coupling during anaesthesia 35–40

Galletly, D. C. *see* Torrance, J. McK., (*C*) 262

Galley, H. F. and Webster, N. R. Midazolam and propofol affect interleukin-8 release from human neutrophils at the post-translational level, (*ARS*) 678–679P

Galley, H. F. *see* Bellamy, M. C. 338–341

Gamondes, J. P. *see* Gressier, M., (*EACTA*) A.78

Garbetta, F. *see* Ranucci, M., (*EACTA*) A.84

Garcia del Valle, S. *see* Marcos, R. C., (*EACTA*) A.80

Garcia-Enguita, M. A. *see* Laglera, S. 671–673

Gareth Jones, J. *see* Byrne, A. J., (*C*) 411

Gargioni, G. *see* Borghi, B. 662–664

Garraffo, R. *see* Isetta, C., (*EACTA*) A.69

Gaukroger, P. B. *see* McKenzie, I., (*R*) 819

Gelman, S. Low-dose dopamine: there is a scientific rationale, (*C*) 546

Gemignani, R. *see* Ruschi, S., (*EACTA*) A.67

Gençelli, J. *see* Çamcý, E., (*EACTA*) A.58

Gentili, M., Houssel, P., Osman, M., Henel, D., Juhel, A. and Bonnet, F. Intra-articular morphine and clonidine produce comparable analgesia but the combination is not more effective 660–661

Germann, R., Haisjackl, M., Schwarz, B., Salak, N., Deusch, E., Pajk, W., Wolf, H. J., Riedmann, B. and Hasibeder, W. Dopamine and intestinal mucosal tissue oxygenation in a porcine model of haemorrhage 357–362

Geskes, G. *see* Langenberg, C. J. M., (*EACTA*) A.50

Giannaris, S., Schorn, B., Wietasch, G., Scholz, M., Buhre, W., Weyland, A. and Hoeft, A. Effect of dexamethasone on oedema formation in patients undergoing coronary bypass surgery, (*EACTA*) A.23

Giannaris, S. *see* Spiegel, T.v., (*EACTA*) A.3

Gilly, H. *see* Mader, N. 125–127

Girard, C. *see* Aouifi, A., (*EACTA*) A.93

Girbes, A. R. J., Hoogenberg, K. and Smit, A. J. "Renal" dopamine, (*C*) 263–264

Girling, D. K. Converting pH and H^+: a rule for the other thumb, (*C*) 410

Girling, K. J., Cavill, G., O'Dwyer, G. and Mahajan, R. P. Effect of 100% oxygen and 50% nitrous oxide on cerebral autoregulation as assessed by the transient hyperaemic response test, (*ARS*) 131P

Giron, G. P. *see* Pittarello, D., (*EACTA*) A.42

Go, G. *see* Sharrock, N. E. 29–34

Goggin, P. *see* Doyle, E., (*R*) 818

Golden, F. St C., Tipton, M. J. and Scott, R. C. Immersion, near-drowning and drowning 214–225

Goldhill, D. R., White, S. A., Owen, N. O. and Hately, W. Ultrasonographic measurement of gastric emptying in volunteers: asessment of technique and effect of low-dose dopamine, (*ARS*) 136P

Goldstein, B. *see* Olsfanger, D. 317–321

Gonzalez, M. *see* Collard, E., (*EACTA*) A.86

Goodman, N. W. *see* Matthews, A. J., (*ARS*) 137P

Gordon, H. *see* Robinson, P. N., (*ARS*) 675–676P

Goto, T., Saito, H., Nakata, Y., Uezono, S., Ichinose, F. and Morita, S. Emergence times from xenon anaesthesia are independent of the duration of anaesthesia 595–599

Gradinac, S. *see* Vuk, Lj., (*EACTA*) A.96

Grana, M. *see* Ruschi, S., (*EACTA*) A.67

Grande, C. M. *see* Zajchuk, R., (*R*) 412–413

Grandy, D. K *see* Hirota, K , (*ARS*) 141P

Graninger, W. *see* La†nigg, A., (*EACTA*) A 21

Graystone, S. J. Continuous intra-arterial blood-gas monitoring, (*C*) 815–816

Greaves, J. D. Anaesthesia and the competence revolution, (*E*) 555–557

Greef, J. *see* Miller, D M., (*ARS*) 682–683P

Greer, R., Pearson, A. J. and Harper, N. J. N. Assessment of neuromuscular monitoring by intensive care nurses: comparison of the TOF-watch and tactile assessment, (*ARS*) 138–139P

Gressier, M., Neidecker, J., Caillet, J B., Boudard, C., Gamondes, J. P , Brune, J., Cordier, J. F. and Lehot, J. J. Perioperative management for lung volume reduction surgery for severe emphysema, (*EACTA*) A.78

Gressier, M *see* Aouifi, A., (*EACTA*) A 91

Grice, A. S. *see* Nielsen, M. S., (*C*) 260

Griffin, M J., Brennan, L. and McShane, A. J. Preoperative education reduces side effects when patient-controlled analgesia is used, (*ARS*) 138P

Griffin, S. C. *see* Bennett, S. R., (*EACTA*) A 13; (*EACTA*) A 18

Griffiths, R., Ionescu, P., Fang, Z., Koblin, D. D. and Eger, E. I. Enhanced choline acetyltransferase activity does not explain the action of inhaled convulsants 389–391

Grimaud, D. *see* Isetta, C., (*EACTA*) A.69

Grinda, J M. *see* Isetta, C., (*EACTA*) A.69

Groener, R and Moyes, D G. Rapid tracheal intubation with propofol, alfentanil and a standard dose of vecuronium 384–385

Groom, P. and Charters, P. Accurate measurement of "true glottic view", (*ARS*) 680–681P

Groom, P., Talbot, J. and Charters, P. Modelling the photographic "restricted window" to derive "true glottic view", (*ARS*) 136P

Grubhofer, G. *see* La†nigg, A., (*EACTA*) A.21

Grzybowski, A. *see* Knapik, P., (*EACTA*) A.94

Gunel, Ö. *see* Erhan, E , (*EACTA*) A.56

Gupta, A. K. *see* Gupta, S , (*ARS*) 680P

Gupta, S , Heath, K. and Matta, B. F. Effect of incremental doses of sevoflurane on cerebral pressure autoregulation in humans 469–472

Gupta, S., Swart, M. L., Al-Rawi, P., Hutchinson, P., Menon, D. K. and Gupta, A. K. Optimal brain tissue oxygenation during hyperventilation in patients with head injuries: measured by a mutliparameter sensor, (*ARS*) 680P

Gupta, S. K *see* Russell, D. 456–459

Gutierrez-Rodriguez, A. *see* Laglera, S. 671–673

Guttmacher, L. B. *see* Nguyen, T. T 801–803

Gwinutt, C. L. *Clinical Anaesthesia*, (*R*) 412

Haas, S. B. *see* Sharrock, N. E 29–34

Haehnel, J. C. *see* Barankay, A., (*EACTA*) A.27

Hagenah, J. U. *see* Weimann, J. 641–644

Hahn, R. G. and Svensén, C Plasma dilution and the rate of infusion of Ringer's solution 64–67

Haisjackl, M. *see* Germann, R. 357–362

Håkanson, E. *see* Svedjeholm, R , (*EACTA*) A.83; Szabo, Z , (*EACTA*) A 72

Hall, A. P. "Ecstacy" and the anaesthetist, (*E*) 697–698

Hall, J. E., Henderson, K. A., Oldham, T. A , Pugh, S. and Harmer, M. Environmental monitoring during gaseous induction with sevoflurane 342–345

Hall, J. E., Oldham, T. A., Stewart, J I. M. and Harmer, M. Comparison between halothane and sevoflurane for adult vital capacity induction 285–288

Hall, W. J. *see* Curran, J. L., (*ARS*) 134P

Halsall, P. J. *see* Curran, J. L., (*ARS*) 134P; Enright, S. M., (*ARS*) 685P

Hancock, P. *see* Paris, S. T. 280–284

Handley, A. J. Basic life support 151–158

Hansen, H. E. *see* de Lasson, L. 719–725

Harada, M. *see* Aoki, H. 476–481

Harmer, M. *see* Hall, J. E. 285–288; 342–345

Harpel, P. C. *see* Sharrock, N. E. 29–34

Harper, N. J N. *see* Greer, R., (*ARS*) 138–139P

Harris, D. *see* Sneyd, J. R. 433–439

Harris, D. N. F. *see* Lockwood, G. G. 581–585; 586–589

Harrison, S. M. *see* Davies, L. A , (*ARS*) 135P

Hartmann, T , Kolev, N., Blaicher, A., Spiss, C. and Zimpfer, M. Validity of acoustic quantification colour kinesis for detection of left ventricular regional wall motion abnormalites: a transoesophageal echocardiographic study 482–487

Hase, I., Oda, Y., Tanaka, K , Mizutani, M., Nakamoto, T. and Asada, A. I.v fentanyl decreases the clearance of midazolam 740–743

Hasibeder, W. *see* Germann, R. 357–362

Hatch, D J. Propofol in paediatric intensive care, (*E*) 274–275

Hatch, D. J. *see* Marsh, D. F. 787–795

Hately, W. *see* Goldhill, D. R., (*ARS*) 136P

Hatherill, M., Tibby, S. M., Durward, A., Rajah, V and Murdoch, I. A. Continuous intra-arterial blood-gas monitoring in infants and children with cyanotic heart disease 665–667

Haussler, J. *see* Dingemanse, J. 567–574

Hawkins, M. and Charters, P. Epiglottis modelling in a computer simulation of difficult laryngoscopy, (*ARS*) 136–137P

Hawksworth, C. R. E. and Serpell, M. G. Anaesthesia with intrathecal ketamine: a dose-finding study, (*ARS*) 674P

Hawksworth, C. R. E , Sivalingham, P and Asbury, A. J. Effect of music on the psychomotor performance of anaesthetists, (*ARS*) 139P

Heath, K *see* Gupta, S. 469–472

Hedenstierna, G. *see* Magnusson, L., (*EACTA*) A.57

Heine, R. *see* Quane, K. A 332–337

Helal, N. *see* Aouifi, A., (*EACTA*) A.93

Hellige, G. *see* Schmidt, W., (*EACTA*) A 64

Hempelmann, G. *see* Ballesteros, M , (*EACTA*) A.19; Boldt, J. 733–739; Welters, I , (*EACTA*) A.22; (*EACTA*) A.71

Henderson, K A. *see* Hall, J. E. 342–345

Henel, D. *see* Gentili, M 660–661

Hentschke, H. *see* Antkowiak, B 617–624

Hering, W *see* Dingemanse, J. 567–574

Hiesmayr, M. *see* Laßnigg, A., (*EACTA*) A.21

Hilditch, G. *see* Inglis, A., (*C*) 263

Hiller, A and Rosenberg, P. H. Transient neurological symptoms after spinal anaesthesia with 4% mepivacaine and 0.5% bupivacaine 301–305

Hindman, B. J *see* Dexter, F 346–351

Hirabayashi, Y., Saitoh, K., Fukuda, H., Igarashi, T., Shimizu, R. and Seo, N. Magnetic resonance imaging of the extradural space of the thoracic spine 563–566

Hirose, M , Hosokawa, T. and Tanaka, Y. Extradural buprenorphine suppresses breast feeding after Caesarean section 120–121

Hirota, K., Appadu, B L., Grandy, D. K., Devi, L A. and Lambert, D. G. Effects of ketamine on cAMP formation in Chinese hamster ovary cells expressing recombinant opioid receptors, (*ARS*) 141P

Hirota, K. *see* Kudo, T. 521–524

Hirst, R. A. *see* Atcheson, R. 78–83

Hitchcock, M. *see* Millar, J. M., (*R*) 818

Hobbhahn, J *see* Frohlich, D. 289–292

Hoche, A., Philipp, E., Schlapp, U., Riedel, W and Karliczek, G. F Effects of dexamethasone on release of endotoxin and cytokines during hypothermic cardiopulmonary bypass, (*EACTA*) A.24

Hoeft, A. *see* Buhre, W. 311–316; Giannaris, S., (*EACTA*) A.23; Spiegel, T.v , (*EACTA*) A.3; Wietasch, G , (*EACTA*) A.59

Hoernecke, R. *see* Doenicke, A. 386–388

Hohn, L *see* Vassalli, F , (*EACTA*) A 79

Holdcroft, A. *see* Deacock, S. 766–769

Holland, R. B. *see* Jones, R. D. M , (*R*) 819

Holper, K. *see* Barankay, A., (*EACTA*) A 27

Hon, L. *see* Schweizer, A., (*EACTA*) A.16

Hood, D. D. *see* Dewan, D. M., (*R*) 147

Hood, P. A. *see* Price Stover, E., (*EACTA*) A.70

Hoogenberg, K. *see* Girbes, A. R J., (*C*) 263–264

Hooper, M. B. Absence of memory for intraoperative information, (*C*) 143

Hopkins, P. M. and Ellis, F. R., (editors) *Hyperthermic and Hypermetabolic Disorders*, (*R*) 266

Hopkins, P. M. *see* Curran, J. L., (*ARS*) 134P; Davies, L. A , (*ARS*) 135P; Enright, S. M , (*ARS*) 685P

Hopton, P. *see* Walsh, T S., (*ARS*) 131–132P

Horie, M. *see* Kurita, T. 770–775

Hormann, Ch. *see* Balogh, D., (*EACTA*) A.26

Hosokawa, T. *see* Hirose, M. 120–121

Houltz, E. *see* Kirno, K., (*EACTA*) A.5, Palmgren, I , (*EACTA*) A.41

Houssel, P. *see* Gentili, M. 660–661

Howard, S. K *see* Gaba, D. M., (*C*) 689–690

Huang, C.-H. *see* Huang, H.-H. 754–758

Huang, H.-H., Chan, H -L., Lin, P.-L., Wu, C.-P. and Huang, C.-H. Time-frequency spectral analysis of heart rate variability during induction of general anaesthesia 754–758

Hultman, J. *see* Palmgren, I., (*EACTA*) A.41

Hund, E. Predominant involvement of motor fibres in patients with critical illness polyneuropathy, (*C*) 548
Hunt, P. *see* Kuter, D. J., (*R*) 413
Hutchinson, P. *see* Gupta, S., (*ARS*) 680P
Hwang, N. C. and Sinclair, M. *Cardiac Anaesthesia: A Practical Handbook*, (*R*) 819–820

Ichinose, F. *see* Goto, T. 595–599
Idvall, J. *see* Bjorkman, S. 575–580
Igarashi, T. *see* Hirabayashi, Y. 563–566
Ihmsen, H. *see* Dingemanse, J. 567–574
Ikeda, K. *see* Katoh, T. 465–468; Kikura, M. 759–765; Kurita, T. 770–775; Moriwaki, G. 782–786
Ikeda, T. *see* Kikura, M. 759–765
Ikeno, S. *see* Nakaigawa, Y. 363–368
Ikuta, Y. *see* Shimoda, O. 714–718
Iles, D. E. *see* Curran, J. L., (*ARS*) 134P
Ilic, V. *see* Jovic, M., (*EACTA*) A.35
Ilkjær, S., Dirks, J., Brennum, J., Wernberg, M. and Dahl, J. B. Effect of systemic N-methyl-D-aspartate receptor antagonist (dextromethorphan) on primary and secondary hyperalgesia in humans 600–605
Imai, H. *see* Aoki, H. 476–481
Inglis, A. and Hilditch, G. "Renal" dopamine, (*C*) 263
Inoue, M. *see* Aoki, H. 476–481
Inoue, S. *see* Nakaigawa, Y. 363–368
Ionescu, P. *see* Griffiths, R. 389–391
Irvine, T. *see* McMahon, C. C., (*EACTA*) A.75
Irving, G. A. and Wallance, M. *Pain Management for the Practising Physician*, (*R*) 265–266
Isayama, S. *see* Shimoda, O. 714–718
Isetta, C., Fischer, F., Garraffo, R., Malzac, B., Grinda, J. M., Jourdan, J. and Grimaud, D. Plasma antifibrinolytic activity after injections of two dosages of tranexamic acid, (*EACTA*) A.69
Ishii, R. *see* Nakaigawa, Y. 363–368

Jakobsen, C.-J. *see* Christiansen, C. L., (*EACTA*) A.55
Jamart, J. *see* Collard, E., (*EACTA*) A.65; (*EACTA*) A.86
Janicke, U. *see* Szekely, A., (*EACTA*) A.15
Jawan, B. *see* Chong, Z.-K. 396–397
Jedeikin, R. *see* Fredman, B. 113–119; (*C*) 688; Olsfanger, D. 317–321
Jenni, R. *see* Schmidlin, D., (*EACTA*) A.38
Jimenez, R. *see* Marcos, R. C., (*EACTA*) A.80
Johnson, C. J. H. *see* Matthews, A. J., (*ARS*) 137P
Johnston, J. R. *see* Loan, P. B., (*ARS*) 684P
Jolin-Mellgård, A. *see* Kieler-Jensen, N., (*EACTA*) A.12
Jones, J. G. *see* Byrne, A. J., (*C*) 690–691; Khan, O. A., (*ARS*) 675P; Swart, M. L., (*ARS*) 677–678P; Taylor, S. R. J., (*ARS*) 674–675P
Jones, P. *see* Manji, M., (*EACTA*) A.87
Jones, R. D. M. and Holland, R. B., (editors) *Anaesthesia and Resuscitation*, (*R*) 819
Jorfeldt, L. *see* Runsio, M., (*EACTA*) A.20
Joris, J., Kaba, A. and Lamy, M. Postoperative spirometry after laparoscopy for lower abdominal or upper abdominal surgical procedures 422–426
Jothilingam, S. *see* Elliott, S. 446–449
Joucken, K. *see* Collard, E., (*EACTA*) A.65; (*EACTA*) A.86
Jourdan, J. *see* Isetta, C., (*EACTA*) A.69
Jovic, M., Popovic, Z., Radomor, B., Bojic, M., Ilic, V., Nezic, D. and Babic, M. Evaluation of left ventricular function by load independent indicators, (*EACTA*) A.35
Jovic, M *see* Vuk, Lj., (*EACTA*) A.96
Jovovic, Lj. *see* Vuk, Lj., (*EACTA*) A.96
Joyce, P. I., Atcheson, R. and Lambert, D. G. Local anaesthetic agents inhibit [^{3}H]noradrenaline uptake into SH-SY5Y human neuroblastoma cells, (*ARS*) 677P
Jozwiak, H. *see* Morton, C. P. J. 3–8
Jude, B. *see* Decoene, C., (*EACTA*) A.66
Juhel, A. *see* Gentili, M. 660–661
Juhl, B. *see* de Lasson, L. 719–725
Juliano, G. *see* Salvi, L., (*EACTA*) A.95
Jung, I. *see* Rauch, H., (*EACTA*) A.2
Juszczyk, G. *see* Knapik, P., (*EACTA*) A.94

Kaba, A. *see* Joris, J. 422–426
Kadziola, Z. *see* Knapik, P., (*EACTA*) A.94
Kalangos, A. *see* Schweizer, A , (*EACTA*) A.16
Kalkman, C. J. *see* Rheineck-Leyssius, A. T. 460–464; Ubags, L. H. 590–594
Kamenik, M. Spinal anaesthesia: effect of the site of injection on the spread of analgesia, (*C*) 144
Kapila, A., Addy, E. V., Verghese, C. and Brain, A. I. J. The intubating laryngeal mask airway: an initial assessment of performance 710–713
Kapila, A. *see* Brain, A. I. J. 699–703; 704–709
Karadeniz, H. *see* Tuğrul, E. 306–310
Karliczek, G. F. *see* Hoche, A., (*EACTA*) A.24; Kraus, B., (*EACTA*) A.34
Kato, S. *see* Kurita, T. 770–775
Katoh, T., Ikeda, K. and Bito, H. Does nitrous oxide antagonize sevoflurane-induced hypnosis? 465–468
Kazmaier, S., Buhre, W., Scholz, M., Weyland, A., Radke, O. and Sonntag, H. Quantitative assessment of inhomogeneity of myocardial blood flow by a single breath inert gas technique. A model study, (*EACTA*) A.33
Kazmaier, S., Rathgeber, J., Buhre, W., Schorn, B., Weyland, A. and Sonntag, H. Influence of ventilation modes on analgesic and sedative demand and pulmonary gas exchange in patients after CABG-surgery, (*EACTA*) A.88
Kazmaier, S. *see* Buhre, W., (*EACTA*) A.4; Weyland, A., (*EACTA*) A.53
Keating, K. E. *see* Quane, K. A. 332–337
Keller, M. *see* Rauch, H., (*EACTA*) A.2
Kellner, J., Winkelbauer, F., Klepetko, W. and Lassnigg, A. Lung transplant oedema: Clinical characteristics and radiological assessment? (*EACTA*) A.81
Kendrick, R. W. *see* Campbell, W. I. 657–659
Kennedy, S. *see* Makin, A., (*ARS*) 687P
Kenny, G. N. C. *see* Russell, D. 456–459
Kerr, C. M. *see* McCourt, K. C., (*ARS*) 134P
Kettler, D. *see* Mohr, M. 253–259; (*C*) 817
Khan, A. *see* Nirmalan, M., (*ARS*) 135P
Khan, O. A., Taylor, S. R. J., Swart, M. and Jones, J. G. Effects of low-dose isoflurane on inhibition of saccadic eye movement, (*ARS*) 675P
Khan, O. A. *see* Taylor, S. R. J., (*ARS*) 674–675P
Khan, Z. P. *see* Mills, G. H. 726–732
Kieler-Jensen, N., Jolin-Mellgård, A., Nordlander, M. and Ricksten, S.-E. Myocardial circulatory and metabolic effects of clevidipine after coronary artery bypass grafting (CABG), (*EACTA*) A.12
Kieler-Jensen, N. *see* Kirno, K., (*EACTA*) A.5
Kikuchi, T., Wang, Y., Shinbori, H., Sato, K. and Okumura, F. Effects of ketamine and pentobarbitone on acetylcholine release from the rat frontal cortex *in vivo* 128–130
Kikura, M., Ikeda, T., Ohnuma, T. and Ikeda, K. Assessment of a new ventricular contractile index obtained with transoesophageal echocardiography before and after cardiopulmonary bypass in cardiac surgical patients 759–765
Kikura, M. *see* Kurita, T. 770–775
Kilger, E. *see* Szekely, A., (*EACTA*) A.15
Kim, D. W. *see* Kim, K. S. 19–23
Kim, K. S., Shim, J. C. and Kim, D. W. Interactions between mivacurium and pancuronium 19–23
Kim, S. C. *see* Kim, S. Y. 379–381
Kim, S. Y., Lee, J. S., Kim, S. C. and Park, W. Twitch augmentation and train-of-four fade during onset of neuromuscular block after subclinical doses of suxamethonium 379–381
King, H.-K. Effects of volume on spinal anaesthesia with 0.25% hyperbaric bupivacaine, (*C*) 262
Kinsella, S. M. Lateral positioning for regional analgesia during labour, (*C*) 260–261
Kirby, R. R., Taylor, R. W. and Civetta, J. M., (editors) *Handbook of Critical Care*, 2nd Edn. (*R*) 147
Kirby, R. R. *see* Civetta, J. M., (*R*) 265
Kirchhoff, K. *see* Leuwer, M., (*ARS*) 132P
Kirchner, E. *see* Leuwer, M., (*ARS*) 132P
Kirimov, U. *see* Mizikov, V., (*EACTA*) A.73
Kirno, K., Kieler-Jensen, N., Houltz, E. and Ricksten, S.-E. The effects of sevoflurane on regional myocardial blood flow and metabolism, when used to control intraoperative hypertension in patients undergoing coronary artery bypass grafting, (*EACTA*) A.5
Kirschfeld, K. *see* Antkowiak, B. 617–624
Kirstetter, P., Lagneau, F., Lucas, O., Krupa, Y. and Marty, J. Role of endothelium in the modulation of isoflurane-induced vasodilatation in rat thoracic aorta 84–87
Kiyama, S. and Takeda, J. Effect of extradural analgesia on the paradoxical arousal response of the electroencephalogram 750–753
Klasing, S. *see* Schwender, D. 53–58
Klein, H. *see* Dresner, M., (*C*) 813
Klepetko, W. *see* Kellner, J., (*EACTA*) A.81
Knapik, P., Wojtalik, M., Grzybowski, A., Kadziola, Z., Banas, S. and Juszczyk, G. Rebound pulmonary

vasoconstriction and desaturation on withdrawal of nitric oxide in infants after cardiac surgery, (*EACTA*) A.94
Kniemeyer, H. *see* Walpoth, B. H., (*EACTA*) A.37
Knothe, C. *see* Ballesteros, M., (*EACTA*) A.19; Welters, I., (*EACTA*) A.22; (*EACTA*) A.71
Kobayashi, A. *see* Aoki, H. 476–481
Koblin, D. D. *see* Griffiths, R. 389–391
Kodakat, S. K. Weaning: is the work of breathing via a tracheostomy tube similar to that via a tracheal tube? (*C*) 814–815
Koga, K., Asai, T., McBeth, C. and Vaughan, R. S. Respiratory complications associated with tracheal intubation and extubation, (*ARS*) 681P
Kokki, H. *see* Nikanne, E. 606–608
Kolano, J. W. *see* Nguyen, T. T. 801–803
Kolev, N. *see* Hartmann, T. 482–487
Kong, A. *see* Absalom, A. R., (*ARS*) 579P
Kotb, H. I. M., El-Kabsh, M. Y., Emara, S. E. S. and Fouad, E. A. Pharmacokinetics of controlled release morphine (MST) in patients with liver cirrhosis 804–806
Kraus, B., Renz, D. and Karliczek, G. F. Near-infrared spectroscopy for testing cerebral CO_2 reactivity, (*EACTA*) A.34
Krivosic-Horber, R. *see* Quane, K. A. 332–337
Krupa, Y. *see* Kirstetter, P. 84–87
Kudo, M. *see* Kudo, T. 521–524
Kudo, T., Kudo, M., Hirota, K. and Lambert, D. G. Studies on the binding of amethocaine to rat cerebrocortical membranes 521–524
Kurita, T., Morita, K., Kato, S., Kikura, M., Horie, M. and Ikeda, K. Comparison of the accuracy of the lithium dilution technique with the thermodilution technique for measurement of cardiac output 770–775
Kurrek, M. and Devitt, J. H. Simulated anaesthetic emergencies, (*C*) 689
Kussman, B., Shorten, G., Uppington, J. and Comunale, M. E. Administration of magnesium sulphate before rocuronium: effects on speed of onset and duration of neuromuscular block 122–124
Kuter, D. J., Hunt, P., Sheridan, W. and Zuker-Franklin, D., (editors) *Thrombopoiesis and Thrombopoietins: Molecular, Cellular, Preclinical and Clinical Biology*, (*R*) 413
Kwiatkowski, D. *see* Borgeat, A. 382–383
Kyttà, J. *see* Laakso, E. 609–611

Laakso, E., Pitkanen, M., Kyttà, J. and Rosenberg, P. H. Knee–chest *vs* horizontal side position during induction of spinal anaesthesia in patients undergoing lumbar disc surgery 609–611
Laglera, S., Garcia-Enguita, M. A., Martinez-Gutierrez, F., Ortega, J. P., Gutierrez-Rodeiguez, A. and Urieta, A. A case of cardiac hydatidosis 671–673
Lagneau, F. *see* Kirstetter, P. 84–87
Lagonidis, D., Matamis, D., Boutel, D., Vakalos, A. and Riggos, D. Transoesophageal echocardiography in the I.C.U. setting: luxury or necessity? (*EACTA*) A.46
Laguardia, A. M. *see* Borghi, B. 662–664
Lamb, F. J. *see* Young, J. D., (*C*) 547
Lambert, D. G. *see* Atcheson, R. 78–83; Hirota, K., (*ARS*) 141P; Joyce, P. I., (*ARS*) 677P; Kudo, T. 521–524; Nicol, B., (*ARS*) 140P
Lamy, M. *see* Joris, J. 422–426
Langenberg, C. J. M., Pietersen, H. G., Geskes, G., De Lange, S. and Soeters, P. Relationship between aortic cross clamp time and myocardial oxygen consumption during coronary artery bypass surgery (CABG), (*EACTA*) A.50
Langford, R. M. *see* Bamigbade, T. A. 352–356
Lappas, D. G. *see* Bakola, A. A., (*EACTA*) A.44
Laroux, M. C. *see* Aouifi, A., (*EACTA*) A.91; (*EACTA*) A.93
Larsen, P. D. *see* Galletly, D. C. 35–40
Lassnigg, A., Presterl, E., Wanzel, O., Mares, P., Grubhofer, G., Graninger, W. and Hiesmayr, M. The proinflammatory cytokine IL-8 is increased after intubation, (*EACTA*) A.21
Lassnigg, A. *see* Kellner, J., (*EACTA*) A.81
Latimer, R. D. *see* Mur, D., (*EACTA*) A.92; Vuylsteke, A., (*EACTA*) A.11
Latronico, N. and Candiani, A. Predominant involvement of motor fibres in patients with critical illness polyneuropathy, (*C*) 547–548
Lattanzio, F. *see* Zuccala, G. 776–781
Lee, A. *see* Walsh, T. S., (*ARS*) 131–132P
Lee, J.-H. *see* Chong, Z.-K. 396–397
Lee, J. S. *see* Kim, S. Y. 379–381
Lehmann-Horn, F. *see* Quane, K. A. 332–337
Lehot, J. J. *see* Aouifi, A., (*EACTA*) A.91; (*EACTA*) A.93; Gressier, M., (*EACTA*) A.78
Lejeune, P. *see* Ewalenko, P. 625–630
Lemoine, E., Aupart, M., Sacher, A., Sirinelli, A., Barrière, J. C., Neville, P. and Marchand, M. Effects of nicardipine on gastric mucosal perfusion during cardiopulmonary bypass, (*EACTA*) A.54
Lentschener, C. and Benhamou, D. Pigs are not human, (*C*) 691–692
Lerou, J. G. C. *see* Vermeulen, P. M. 488–496
Lesclerc, G. *see* Troncy, E. 631–640
Leunens, V. *see* Raez, R., (*EACTA*) A.47
Leuwer, M., Thum, P., Kirchhoff, K., Bornscheuer, A., Seitz, W., Piepenbrock, S. and Kirchner, E. No direct effects of dopexamine on the isolated perfused rat kidney, (*ARS*) 132P
Levin, D. L. and Morriss, F. C., (editors) *Essentials of Pediatric Intensive Care*, 2nd Edn, (*R*) 818–819
Lewer, B. M. F. *see* Torrance, J. McK., (*C*) 262
Licker, M. *see* Schweizer, A., (*EACTA*) A.16; Vassalli, F., (*EACTA*) A.79
Lienhart, A. *see* Camus, Y. 796–797
Lillywhite, N. *see* Wilson, C. M., (*ARS*) 139–140P
Lin, P.-L. *see* Huang, H.-H. 754–758
Lintner, A. *see* Skarvan, K., (*EACTA*) A.39
Loan, P. B., Symington, M. J., Mirakhur, R. K., Johnston, J. R., Trinder, T. J. and Patterson, C. J. Effect of neuromuscular block using vecuronium on oxygen consumption in critically ill adults, (*ARS*) 684P
Lockwood, G. G., Dob, D. P., Bryant, D. J., Wilson, J. A., Sargentoni, J., Sapsed-Byrne, S. M., Harris, D. N. F. and Menon, D. K. Magnetic resonance spectroscopy of isoflurane kinetics in humans. Part I: elimination from the head 581–585; Magnetic resonance spectroscopy of isoflurane kinetics in humans. Part II: functional localization 586–589
Lockwood, G. G., Sapsed-Byrne, S. M. and Smith, M. A. Effect of temperature on the solubility of desflurane, sevoflurane, enflurane and halothane in blood 517–520
Loughnan, B. A. *see* Robinson, P. N., (*ARS*) 675–676P
Lowe, D. *see* MacKinnon, K. L., (*ARS*) 678P; Molnar, Z., (*ARS*) 678P
Lowry, D. *see* Carroll, M. T., (*ARS*) 683P
Lucas, O. *see* Kirstetter, P. 84–87
Ludbrook, G. L. and Upton, R. N. A physiological model of induction of anaesthesia with propofol in sheep. 2. Model analysis and implications for dose requirements 505–513
Ludbrook, G. L. *see* Upton, R. N. 497–504
Lundberg, D. B. A. *see* Mueller, R. A., (*R*) 265
Lustik, S. J. *see* Nguyen, T. T. 801–803

Ma, D., Sapsed-Byrne, S., Chakrabarti, M. K. and Whitwam, J. G. Effect of sevoflurane on spontaneous sympathetic activity and baroreflexes in rabbits, (*ARS*) 141–142P
Ma, D., Sapsed-Byrne, S. M., Chakrabarti, M. K. and Whitwam, J. G. Synergistic effect of fentanyl and midazolam on phrenic nerve activity in rabbits, (*ARS*) 686–687P
Ma, D., Wang, C., Pac-Soo, C. K., Chakrabarti, M. K. and Whitwam, J. G. Dissociation between the effect of nitrous oxide on spontaneous and reflexly evoked sympathetic activity in dogs 525–529
McBeth, C. *see* Koga, K., (*ARS*) 681P
McCarthy, T. V. *see* Quane, K. A. 332–337
McCaughey, W., Clarke, R. S. J., Fee, J. P. H. and Wallace, W. F. M., (editors) *Anaesthetic Physiology and Pharmacology*, (*R*) 820
McCawley, C. *see* Bakola, A. A., (*EACTA*) A.44
McClure, J. H. *see* Dickson, M. A. S. 297–300; McCrae, A. F. 558–562; Morton, C. P. J., (*C*) 813
McCourt, K. C., Salmela, L., Carroll, M., Kerr, C. M., Mirakhur, R. K. and Olkkola, K. T. Comparison of rocuronium and suxamethonium for use during rapid sequence induction of anaesthesia, (*ARS*) 134P
McCourt, K. C. *see* Carroll, M. T., (*ARS*) 683P
McCrae, A. F., Westerling, P. and McClure, J. H. Pharmacokinetic and clinical study of ropivacaine and bupivacaine in women receiving extradural analgesia in labour 558–562
McKeague, H. and Cunningham, A. J. Postoperative respiratory dysfunction: is the site of surgery crucial? (*E*) 415–416
McKenzie, I., Gaukroger, P. B., Ragg, P. and Brown, T. C. K. (Kester), (editors) *Manual of Acute Pain Management in Children*, (*R*) 819
McKeown, A. J. P. *see* Bennett, S. R., (*EACTA*) A.13; (*EACTA*) A.18

MacKinnon, K. L., Molnar, Z., Watson, I. D., Shearer, E. and Lowe, D. Use of microalbuminuria as an indicator for the development of sepsis and multiple system organ failure, (*ARS*) 678P

MacLaren, A. J., Pierce, M. M. T. and Albano, J. D. M. Plasma bradykinin during cardiopulmonary bypass and the effect of angiotensin converting enzyme inhibition, (*EACTA*) A.17

MClure, J. H. *see* Morton, C. P. J. 3–8

McMahon, C. C., Irvine, T. and Conacher, I. D. Transoesophageal echocardiography of the right ventricle in thoracic patients, (*EACTA*) A.75

McShane, A. J. *see* Griffin, M. J., (*ARS*) 138P

Mader, N., Gilly, H. and Bittner, R. E. Dystrophin deficient *mdx* muscle is not prone to MH susceptibility: an *in vitro* study 125–127

Magnusson, A. *see* Morton, C. P. J. 3–8

Magnusson, L., Zemgulis, V., Tenling, A., Wernlund, J , Tydén, H., Thelin, S. and Hedenstierna, G. Efficacy of a vital capacity manœuvre to prevent post-cardiopulmonary bypass atelectasis: An experimental study, (*EACTA*) A.57

Mahajan, R. P. *see* Girling, K. J., (*ARS*) 131P

Mair, J. *see* Balogh, D., (*EACTA*) A.26

Mair, P. *see* Balogh, D., (*EACTA*) A.26

Makin, A., Basler, M., Serpell, M., Kennedy, S., Bolton, P. and Carson, D. I.v. regional anaesthesia. Comparison of 0.25% prilocaine with or without 5% dextrose, (*ARS*) 687P

Malzac, B. *see* Isetta, C., (*EACTA*) A.69

Mamet, J. P. *see* Diemunsch, P. 322–326

Manji, M., Ariffin, S. and Faroqui, M. Preoperative ACE inhibition and vasoconstrictor requirements post cardiopulmonary bypass, (*EACTA*) A.14

Manji, M., Rigg, C., Jones, P., Ariffin, S. and Faroqui, M. Tramadol for post operative analgesia in coronary artery bypass graft surgery, (*EACTA*) A.87

Manning, B. M. *see* Quane, K. A. 332–337

Mapleson, W. W. *see* Asai, T., (*ARS*) 133P; (*ARS*) 133P; (*ARS*) 676P; Couto da Silva, J. M. 103–112

Marcassa, A. *see* Pittarello, D., (*EACTA*) A.42

Marchand, M. *see* Lemoine, E., (*EACTA*) A.54

Marcos, R. C., Garcia del Valle, S., Jimenez, R. and Muñoz, L. Results in five patients undergoing pulmonary thromboendarterectomy, (*EACTA*) A.80

Mareels, K. *see* Foubert, L., (*EACTA*) A.90

Mares, P. *see* La†nigg, A., (*EACTA*) A.21

Margreiter, J. *see* Balogh, D., (*EACTA*) A.26

Marine, J. J. *see* Perret, C., (*R*) 266

Maritti, M. *see* Della Rocca, G., (*EACTA*) A.77

Markham, A. F. *see* Curran, J. L., (*ARS*) 134P

Marquette, C. H. *see* Ausseur, A., (*EACTA*) A.74

Marsh, D. F , Hatch, D. J. and Fitzgerald, M. Opioid systems and the newborn 787–795

Martin, E. *see* Bottiger, R. H , (*EACTA*) A.32, Rauch, H., (*EACTA*) A.2

Martin, J. T. and Warner, M. A., (editors) *Positioning in Anesthesia and Surgery*, 3rd Edn, (*R*) 693

Martin, K. *see* Szekely, A., (*EACTA*) A.15

Martin, P. H., Murthy, B. V. S. and Petros, A. J. Metabolic, biochemical and haemodynamic effects of infusion of propofol for long-term sedation of children undergoing intensive care 276–279

Martinez-Gutierrez, F. *see* Laglera, S. 671–673

Marty, J. *see* Kirstetter, P. 84–87

Matamis, D. *see* Lagonidis, D., (*EACTA*) A.46

Matta, B. F. *see* Gupta, S. 469–472

Matthews, A. J., Johnson, C. J. H. and Goodman, N. W. Body posture during simulated tracheal intubation, (*ARS*) 137P

Mayer, M. *see* Doenicke, A. 386–388

Mazzoni, M. *see* Salvi, L., (*EACTA*) A.95

McQuillan, P. J. *see* Burden, R. J., (*e*) 413

Meakin, G. *see* Meretoja, O. A., (*ARS*) 683–684P

Mecklenburgh, J. S. *see* Wilkes, A. R., (*ARS*) 681–682P

Meineke, I. *see* Schmidt, W , (*EACTA*) A.64

Meisner, H *see* Barankay, A., (*EACTA*) A.27

Menges, T. *see* Welters, I., (*EACTA*) A.22; (*EACTA*) A.71

Menon, D. K. *see* Gupta, S., (*ARS*) 680P; Lockwood, G. G. 581–585; 586–589

Meretoja, O. A., Meakin, G., Taivainen, T., Perkins, R. J., Wirtavuori, K., Murphy, A. K. and Raiha, L Cardiovascular effects and time-course of action of cisatracurium in infants and children during thiopentone–alfentanil–nitrous oxide–oxygen anaesthesia, (*ARS*) 683–684P

Meyns, B. *see* Raez, R., (*EACTA*) A.47

Mezin, P., Payen, J -F., Bosson, J.-L., Brambilla, E. and Stieglitz, P. Histological support for the difference between malignant hyperthermia susceptible (MHS), equivocal (MHE) and negative (MHN) muscle biopsies 327–331

Michalis, A. S. *see* Nicolaides, A., (*EACTA*) A.45

Michalopoulos, A. *see* Papadimitriou, L , (*EACTA*) A.51

Michalopouolos, N. *see* Nicolaides, A., (*EACTA*) A.45

Mielck, F., Stephan, H., Buhre, W., Weyland, A. and Sonntag, H. Influence of sevoflurane on cerebral metabolism, blood flow and CO_2-reactivity, (*EACTA*) A.6

Millar, J. M., Rudkin, G. E. and Hitchcock, M. *Practical Anaesthesia and Analgesia for Day Surgery*, (*R*) 818

Miller, D. M., Greef, J. and Wessels, J. A. Estimation of cardiac output using the Maxima breathing system, (*ARS*) 682–683P

Miller, J. D. *see* Souter, M. J. 97–102

Mills, G. H., Khan, Z. P., Moxham, J., Desai, J., Forsyth, A. and Ponte, J. Effects of temperature on phrenic nerve and diaphragmatic function during cardiac surgery 726–732

Mills, P *see* Wilson, C M., (*ARS*) 139–140P

Mirakhur, R. K. *see* Carroll, M. T., (*ARS*) 683P; Loan, P. B., (*ARS*) 684P; McCourt, K. C., (*ARS*) 134P

Miric, M. *see* Vuk, Lj., (*EACTA*) A.96

Mizikov, V., Variushina, T. and Kirimov, U. The laryngeal mask for fibreoptic bronchoscopy in children, (*EACTA*) A.73

Mizobe, T. *see* Aoki, H. 476–481

Mizutani, M. *see* Hase, I. 740–743

Mohacsi, P. *see* Walpoth, B. H., (*EACTA*) A.30

Mohr, M. and Kettler, D. Ethical aspects of resuscitation 253–259; The future of ethical treatment, (*C*) 817

Molnar, Z. and Charters, P. Lanz tube as alternative for ICU hyperbaric oxygen therapy, (*ARS*) 679–680P

Molnar, Z., Shearer, E. and Lowe, D. *N*-acetylcysteine in multisystem organ failure, (*ARS*) 678P

Molnar, Z. *see* MacKinnon, K. L., (*ARS*) 678P

Montebugnoli, M. *see* Borghi, B. 662–664

Moores, C. *see* Dickson, M. A. S. 297–300

Morita, K. *see* Kurita, T. 770–775

Morita, S. *see* Goto, T. 595–599

Moriwaki, G., Bito, H. and Ikeda, K. Partly exhausted soda lime or soda lime with water added, inhibits the increase in compound A concentration in the circle system during low-flow sevoflurane anaesthesia 782–786

Morley, A. P. External cooling in critically ill febrile ICU patients, (*C*) 546–547

Morricone, L. *see* Ranucci, M., (*EACTA*) A.84

Morris, A *see* Srinivasa, R., (*ARS*) 686P

Morris, M. J. Improved intraoperative assessment of aortic stentless valves using transoeosophageal echocardiography, (*EACTA*) A.43

Morriss, F. C. *see* Levin, D. L., (*R*) 818–819

Morton, C. P. J., Bloomfield, S., Magnusson, A., Jozwiak, H. and MClure, J. H. Ropivacaine 0.75% for extradural anaesthesia in elective Caesarean section: an open clinical and pharmacokinetic study in mother and neonate 3–8

Morton, C. P. J. and McClure, J. H. Ropivacaine test dose in extradural anaesthesia, (*C*) 813

Morton, N. S., Pollack, M. M. and Wallace, P. G. M., (editors) *Stabilisation and Transport of the Critically Ill*, (*R*) 267

Mostafa, S. M. and Atherton, A. M. J. Sevoflurane for difficult tracheal intubation 392–393

Motsch, B. W. *see* Bottiger, R. H., (*EACTA*) A.32

Motsch, J. *see* Rauch, H., (*EACTA*) A.2; Weimann, J. 641–644

Moxham, J *see* Mills, G. H. 726–732

Moyes, D. G. *see* Groener, R. 384–385

Muchada, R. *see* Tournadre, J. P. 514–516

Mueller, R. A. and Lundberg, D. B. A. *Manual of Drug Interactions for Anesthesiology*, 3rd Edn, (*R*) 265

Muller, J. *see* Bottiger, R. H., (*EACTA*) A.32

Muller, L. *see* Balogh, D., (*EACTA*) A.26

Müller, M. *see* Boldt, J. 733–739

Müller, S. *see* Schmidt, W., (*EACTA*) A.64

Muñoz, L. *see* Marcos, R. C., (*EACTA*) A.80

Mur, D., Vuylsteke, A., Powroznyk, A., Oduro, A. and Latimer, R. D. Evaluation of two "universal" nitric oxide delivery systems, (*EACTA*) A.92

Murdoch, I. A. *see* Hatherill, M. 665–667

Murphy, A. K. *see* Meretoja, O. A., (*ARS*) 683–684P

Murray, A. *see* Prosser, D. P. 293–296

Murray, M., Coursin, D., Pearl, R. and Prough, D., (editors) *Critical Care Medicine: Perioperative Management*, (*R*) 267

Murthy, B. V. S. *see* Martin, P. H. 276–279

Mushambi, M. C. *see* Elton, C D., (*E*) 551–554

Naeije, R. *see* Ewalenko, P. 625–630
Naguib, M., Samarkandi, A. H., Ammar, A. and Turkistani, A. Comparison of suxamethonium and different combinations of rocuronium and mivacurium for rapid tracheal intubation in children 45[illegible]–455
Nakaigawa, Y., Akazawa, S., Shimizu, R., Ishii, R., Ikeno, S., Inoue, S and Yamato, R. Effects of magnesium sulphate on the cardiovascular system, coronary circulation and myocardial metabolism in anaesthetized dogs 363–368
Nakamoto, T. *see* Hase, I. 740–743
Nakata, Y. *see* Goto, T. 595–599
Nakatsuka, M. and Frederick, L. A Change in extravascular lung water after re-expansion of the collapsed lung in sheep measured by the thermo-saline dilution method, (*EACTA*) A.76
Nathwani, D. *see* Sharpe, R. M., (*C*) 410–411
Neidecker, J. *see* Aouifi, A., (*EACTA*) A.91; (*EACTA*) A.93; Gressier, M., (*EACTA*) A.78
Nettelblad, H. *see* Bengtsson, M. 668–670
Neville, P. *see* Lemoine, E., (*EACTA*) A.54
Newman, D J. *see* Tupper-Carey, D. A , (*EACTA*) A.29
Newton, D. E. F. *see* Sharpe, R. M., (*C*) 410–411
Nezic, D. *see* Jovic, M., (*EACTA*) A.35
Nguyen, T. T., Chhibber, A. K., Lustik, S. J., Kolano, J. W., Dillon, P. J. and Guttmacher, L. B. Effect of methohexitone and propofol with or without alfentanil on seizure duration and recovery in electroconvulsive therapy 801–803
Nicol, B., Rowbotham, D. J. and Lambert, D. G. Halothane decreases K$^+$ evoked glutamate release from rat cerebrocortical slices, (*ARS*) 140P
Nicolaides, A , Paraskevaides, I., Deligianni, M., Dimitriou, S., Michalopouolos, N., Papadimitriou, L. and Michalis, A S. Comparison of propofol-fentanyl and isoflurane-fentanyl anaesthesia with transoesophageal echocardiography for coronary artery bypass graft surgery, (*EACTA*) A.45
Nielsen, M. S and Grice, A. S. Oxygenation criteria—a plea for more information, (*C*) 260
Nightingale, P. *see* Nirmalan, M., (*ARS*) 135P
Nikanne, E., Kokki, H. and Tuovinen, K. Comparison of perioperative ketoprofen 2.0 mg kg^{-1} with 0.5 mg kg^{-1} i.v in small children during adenoidectomy 606–608
Nikolaidis, A. *see* Papadimitriou, L., (*EACTA*) A.51
Nilsson, F. *see* Westerlind, A., (*EACTA*) A 82
Ninet, J. *see* Aouifi, A., (*EACTA*) A.[illegible]1
Nirmalan, M., Willard, T., Khan, A. and Nightingale, P. Effect of assuming a fixed $(Ca_{O_2} - C\bar{v}_{O_2})$ on shunt calculations, (*ARS*) 135P
Nishimura, Y. *see* Raez, R., (*EACTA*) A.47
Nolan, J. P. and Parr, M. J. A. Aspects of resuscitation in trauma 226–240
Nollert, G. *see* Szekely, A., (*EACTA*) A.15
Nordlander, M. *see* Kieler-Jensen, N., (*EACTA*) A.12
Noreng, M. *see* Christiansen, C. L., (*EACTA*) A.55
Nottrott, M. *see* Schmidt, W., (*EACTA*) A.64
Novak-Jankoviè, V , Paver-Erzen, V , Osredkar, J., Oberauner, L. and Pozlep, G. Clonidine and neuroendocrine stress response during lung surgery, (*EACTA*) A.9

Obal, D *see* Schlack, W 88–96
O'Beirne, H. A., Young, Y., Thornton, J and Bellamy, M. C. Desflurane *vs* isoflurane in liver transplantation: a comparison of outcomes, (*ARS*) 132P
Oberauner, L. *see* Novak-Jankoviè, V., (*EACTA*) A.9
O'Connor, P. J., Welsh, K. R., Cross, M. H and Shah, M. V. Awake or asleep pulmonary artery catheter insertion? A comparison of catecholamine and haemodynamic responses, (*EACTA*) A.31
Oda, Y. *see* Hase, I. 740–743
Oduro, A. *see* Mur, D., (*EACTA*) A.92; Vuylsteke, A., (*EACTA*) A.11
O'Dwyer, G. *see* Girling, K. J., (*ARS*) 131P
Oh, T. E , (editor) *Intensive Care Manual*, 4th Edn, (*R*) 266–267
Ohnuma, T. *see* Kikura, M. 759–765
Okumura, F *see* Kikuchi, T 128–130
Oldham, T. A. *see* Hall, J. E 285–288 342–345
Olkkola, K. T *see* McCourt, K. C., (*ARS*) 134P
Olsfanger, D , Fredman, B., Goldsteen, B., Shapiro, A. and Jedeikin, R. Acute normovolaemic haemodilution decreases postoperative allogeneic blood transfusion after total knee replacement 317–321
Olsfanger, D. *see* Fredman, B. 113–11[illegible]; (*C*) 688
Ording, H. *see* Quane, K. A 332–337
Ortega, J. P. *see* Laglera, S. 671–673
Osman, M. *see* Gentili, M. 660–661
Osredkar, J. *see* Novak-Jankoviè, V., (*EACTA*) A.9
Osselaer, J. C. *see* Collard, E., (*EACTA*) A.65
Ostwald, P. *see* Doenicke, A. 386–388
Öwall, A. *see* Runsio, M., (*EACTA*) A.20
Owen, N. O. *see* Goldhill, D R., (*ARS*) 136P
Ozaki, S. *see* Raez, R., (*EACTA*) A.47
Özbaran, M. *see* Erhan, E., (*EACTA*) A.56
Özuner, Z *see* Suzer, Ö., (*EACTA*) A.1

Paaske, W P. *see* de Lasson, L. 719–725
Pac-Soo, C. K. *see* Ma, D. 525–529
Paes, M L. *see* Sammut, M. S 810–812
Pahor, M. *see* Zuccala, G. 776–781
Pajk, W. *see* Germann, R. 357–362
Pal, S. K. *see* Sharpe, R. M., (*C*) 410–411
Palmgren, I., Hultman, J. and Houltz, E. Perioperative transoesophageal echocardiography with low dose dobutamine: A feasible test for viability? (*EACTA*) A.41
Papadimitriou, L., Deligianni, M., Smyrli, A., Antzaka, Ch., Nikolaidis, A., Dimitriou, St., Rellia, P. and Michalopoulos, A. Significance of regional cerebral oxygen saturation (rSO$_2$) during open heart surgery, (*EACTA*) A.51
Papadimitriou, L. *see* Nicolaides, A., (*EACTA*) A.45
Papsdorf, D *see* Boldt, J. 733–739
Paraskevaides, I. *see* Nicolaides, A., (*EACTA*) A.45
Paris, A. *see* Scholz, J., (*EACTA*) A.7
Paris, S. T., Cafferkey, M., Tarling, M., Hancock, P., Yate, P. M. and Flynn, P J Comparison of sevoflurane and halothane for outpatient dental anaesthesia in children 280–284
Park, W. *see* Kim, S. Y. 379–381
Parr, M J. A. *see* Nolan, J. P. 226–240
Parry-Jones, A. J. D. Thorascopic sympathectomy, (*C*) 688
Parschalk, P. *see* Bartunek, A., (*EACTA*) A 62
Pasch, T. *see* Zollinger, A. 47–52; (*C*) 816–817
Pasini, L. *see* Pittarello, D., (*EACTA*) A.42
Patterson, C. J. *see* Loan, P. B., (*ARS*) 684P
Paver-Erzen, V. *see* Novak-Jankoviè, V., (*EACTA*) A 9
Payen, J.-F. *see* Mezin, P. 327–331
Pearl, R. *see* Murray, M., (*R*) 267
Pearson, A. J., Pomfrett, C. J. D and Pollard, B. J. Does the insertion of earplugs affect the bispectral index of the sedated patient in the intensive care unit? (*ARS*) 685–686P
Pearson, A. J. *see* Greer, R , (*ARS*) 138–139P
Pedersen, E. B. *see* de Lasson, L. 719–725
Peek, G. J. and Firmin, R. K Oxygenation criteria—a plea for more information, (*C*) 260
Pembeci, K. *see* Çamcý, E , (*EACTA*) A 58
Pembecİ, K. *see* Tuğrul, E. 306–310
Peric, M. *see* Vuk, Lj., (*EACTA*) A.96
Perkins, R. J. *see* Meretoja, O A., (*ARS*) 683–684P
Pernersdorfer, T *see* Bartunek, A., (*EACTA*) A.62
Perret, C., Tagan, D., Feihl, F. and Marine, J. J. *The Pulmonary Artery Catheter in Critical Care—A Concise Handbook*, (*R*) 266
Perryman, R. *see* Wang, N., (*EACTA*) A.63
Peter, K. *see* Schwender, D. 53–58
Petros, A. J. *see* Martin, P. H. 276–279
Peyton, R. *see* Skinner, D , (*R*) 147
Philipp, E. *see* Hoche, A., (*EACTA*) A 24
Piepenbrock, S. *see* Leuwer, M., (*ARS*) 132P
Pierce, M. M. T. *see* MacLaren, A. J., (*EACTA*) A.17
Pietersen, H G. *see* Langenberg, C. J. M., (*EACTA*) A.50
Pignotti, E. *see* Borghi, B. 662–664
Pigott, D *see* Piriou, V. 68–77
Pinsky, M. R , (editor) *Applied Cardiovascular Physiology. (Update in Intensive Care and Emergency Medicine Series)*, (*R*) 549
Pinsky, M. R., Dhainaut, J.-F. and Artigas, A., (editors) *The Pulmonary Circulation · Moving From Passive to Active Control*, (*R*) 266
Piper, I R. *see* Souter, M. J. 97–102
Piriou, V., Ross, S., Pigott, D , Evans, R. and Foex, P. Beneficial effect of concomitant administration of isoflurane and nicorandil 68–77
Pitkanen, M *see* Laakso, E. 609–611
Pittarello, D., Sorbara, C., Botanto, R , Armellin, G., Marcassa, A., Pasini, L. and Giron, G. P. Transoesophageal echocardiography of mitral and pulmonary venous flow as estimation of diastolic function, (*EACTA*) A.42
Pledger, D R. *see* Absalom, A. R., (*ARS*) 679P
Plowman, A., Barson, J., Clarke, J. and Bolsin, S. Sevoflurane or halothane for paediatric endoscopy, (*C*) 143–144

Pollack, M. M. *see* Morton, N. S., (*R*) 267
Pollard, B. J. *see* Pearson, A. J., (*ARS*) 685–686P
Pomfrett, C. J. D. *see* Pearson, A. J., (*ARS*) 685–686P
Pompei, L. *see* Della Rocca, G., (*EACTA*) A.77
Ponte, J. *see* Mills, G. H. 726–732
Poon, Y.-Y. *see* Chong, Z.-K. 396–397
Popovic, Z. *see* Jovic, M., (*EACTA*) A.35
Power, I. *see* Asai, T., (*ARS*) 133P; (*ARS*) 133P; (*ARS*) 676P
Powroznyk, A. *see* Mur, D., (*EACTA*) A.92
Pozlep, G. *see* Novak-Jankoviè, V., (*EACTA*) A.9
Pozzi, M. *see* Cheung, S. L. W. 9–13
Prat, A. *see* Decoene, C., (*EACTA*) A.66
Preckel, B. *see* Schlack, W. 88–96
Preis, C. A. and Preis, I. S. Obstruction of the lumen of a plastic 15-mm connector inserted into a cut paediatric tube—Is it possible to avoid this damage? (*C*) 692
Preis, I. S. *see* Preis, C. A., (*C*) 692
Presterl, E. *see* La†nigg, A., (*EACTA*) A.21
Price, C. P. *see* Tupper-Carey, D. A., (*EACTA*) A.29
Price Stover, E., Siegel, L. C. and Hood, P. A. Platelet-rich plasmapheresis reduces allogeneic platelet transfusions and cost in complex cardiac surgery, (*EACTA*) A.70
Printzen, G. *see* Walpoth, B. H., (*EACTA*) A.30
Prosser, D. P., Davis, A., Booker, P. D. and Murray, A. Caudal tramadol for postoperative analgesia in paediatric hypospadias surgery 293–296
Prough, D. *see* Murray, M., (*R*) 267
Pugh, S. *see* Hall, J. E. 342–345
Pugliese, F. *see* Della Rocca, G., (*EACTA*) A.77
Puschendorf, B. *see* Balogh, D., (*EACTA*) A.26

Quane, K. A., Ording, H., Keating, K. E., Manning, B. M., Heine, R., Bendixen, D., Berg, K., Krivosic-Horber, R., Lehmann-Horn, F., Fagerlund, T. and McCarthy, T. V. Detection of a novel mutation at amino acid position 614 in the ryanodine receptor in malignant hyperthermia 332–337

Radke, O. *see* Kazmaier, S., (*EACTA*) A.33
Radojevic, D. *see* Vuk, Lj., (*EACTA*) A.96
Radomir, B. *see* Vuk, Lj., (*EACTA*) A.96
Radomor, B. *see* Jovic, M., (*EACTA*) A.35
Rae, S. M. and Wildsmith, J. A. W. So just who was James "Young" Simpson? (*E*) 271–273
Raez, R., Nishimura, Y., Meyns, B., Ozaki, S., Leunens, V. and Flameng, W. An experimental model of chronic myocardial hibernation in sheep, (*EACTA*) A.47
Ragg, P. *see* McKenzie, I., (*R*) 819
Raiha, L. *see* Meretoja, O. A., (*ARS*) 683–684P
Rajah, V. *see* Hatherill, M. 665–667
Ramasamy, D. and Eadie, R. Transient radicular irritation after spinal anaesthesia with 2% isobaric lignocaine 394–395
Ranocchi, R. *see* Borghi, B. 662–664
Ranucci, M., Cirri, S., Soro, G., Cazzaniga, A., Garbetta, F., Morricone, L., Enrini, R. and Caviezel, F. Is severe obesity a risk factor for coronary surgery? (*EACTA*) A.84
Ranucci, M., Cirri, S., Soro, G., Conti, D. and Cazzaniga, A. Normothermic perfusion: effects on postoperative multi-organ dysfunction, (*EACTA*) A.85
Raphael, J. H. and Butt, M. W. Comparison of isoflurane with propofol on respiratory cilia 473–475
Rathgeber, J. *see* Kazmaier, S., (*EACTA*) A.88
Rauch, H., Motsch, J., Jung, I., Engelmann, E., Keller, M and Martin, E. Cisatracurium vs pancuronium for neuromuscular blockade in patients undergoing coronary revascularisation, (*EACTA*) A.2
Rees, P. H. *see* Russell, D. 456–459
Reich, D. L. *see* Ammar, T., (*EACTA*) A.68
Reichenspurner, H. *see* Walpoth, B. H., (*EACTA*) A.30
Reitz, B. *see* Walpoth, B. H., (*EACTA*) A.30
Rellia, P. *see* Papadimitriou, L., (*EACTA*) A.51
Renz, D. *see* Kraus, B., (*EACTA*) A.34
Rheineck-Leyssius, A. T. and Kalkman, C. J. Influence of pulse oximeter lower alarm limit on the incidence of hypoxaemia in the recovery room 460–464
Rhodes, A. *see* Young, J. D., (*C*) 547
Richardson, C. Management of the airway and ventilation during resuscitation, (*C*) 814
Richardson, M. G. and Wissler, R. N. Lateral positioning for regional analgesia during labour, (*C*) 261–262
Richter, J. A. *see* Barankay, A., (*EACTA*) A.27
Ricksten, S.-E. *see* Kieler-Jensen, N., (*EACTA*) A.12; Kirno, K., (*EACTA*) A.5; Westerlind, A., (*EACTA*) A.82
Riedel, W. *see* Hoche, A., (*EACTA*) A.24
Riedmann, B. *see* Germann, R. 357–362
Rigemar, G. *see* Bjórkman, S. 575–580
Rigg, C. *see* Manji, M., (*EACTA*) A.87
Riggos, D. *see* Lagonidis, D., (*EACTA*) A.46
Righi, U. *see* Borghi, B. 662–664
Rijckaert, D. *see* Foubert, L., (*EACTA*) A.90
Risdall, J. *see* Swart, M. L., (*ARS*) 677–678P
Roberts, C. *see* Skinner, D., (*R*) 147
Roberts, M. *see* Young, J. D. 398–401
Robertson, C. E. Advanced life support guidelines 172–177
Robinson, P. N., Romney, M., Gordon, H. and Loughnan, B. A. Outcome of labour using low-dose extradural bupivacaine compared with intramuscular pethidine, (*ARS*) 675–676P
Robinson, R. L. *see* Curran, J. L., (*ARS*) 134P
Rodola, S. *see* Zuccala, G. 776–781
Rohlfs, R. *see* Seeberger, M. D., (*EACTA*) A 40
Roizen, M. F. *see* Doenicke, A. 386–388
Rolly, G. *see* Foubert, L., (*EACTA*) A.90
Rombaut, A. *see* Verborgh, C., (*EACTA*) A.10
Romer, H. C. and Russell, G. N. A survey of the practice of thoracic epidural analgesia in the United Kingdom, (*EACTA*) A.89
Romney, M. *see* Robinson, P. N., (*ARS*) 675–676P
Rosenberg, P. H. *see* Hiller, A 301–305
Rosenberg, P. H. *see* Laakso, E. 609–611
Rosenqvist, M. *see* Runsiò, M., (*EACTA*) A.20
Rosenthaler, C. *see* Seeberger, M. D., (*EACTA*) A.40
Ross, S. *see* Piriou, V. 68–77
Roth, S. H. *see* Archer, D. P. 744–749
Rowbotham, D. J. *see* Atcheson, R. 78–83; Nicol, B., (*ARS*) 140P
Royston, D. *see* Russell, D. 456–459
Ruberto, F. *see* Della Rocca, G., (*EACTA*) A.77
Rudkin, G. E. *see* Millar, J. M., (*R*) 818
Runsio, M., Bergfeld, L., Rosenqvist, M., Òwall, A. and Jorfeldt, L. Changes in human coronary sinus blood flow and myocardial metabolism induced by ventricular fibrillation and defibrillation, (*EACTA*) A.20
Ruschi, S., Grana, M., Gemignani, R., Russo, V., Salerno, L., Comite, C., Stefani, M., Troiani, R. and Bortolotti, U. A single dose of aprotinin or tranexamic acid in CPB priming reduces blood loss in primary cardiac surgery for coronary disease, (*EACTA*) A 67
Russell, D., Royston, D., Rees, P. H., Gupta, S. K. and Kenny, G. N. C. Effect of temperature and cardiopulmonary bypass on the pharmacokinetics of remifentanil 456–459
Russell, G. N. *see* Romer, H. C., (*EACTA*) A.89
Russell, I. F. *see* Wang, M., (*C*) 143
Russo, V. *see* Ruschi, S., (*EACTA*) A.67

Sacher, A. *see* Lemoine, E., (*EACTA*) A.54
Saito, H. *see* Goto, T. 595–599
Saitoh, K. *see* Hirabayashi, Y. 563–566
Sakamoto, M. *see* Shimoda, O. 714–718
Sakarya, M. *see* Aþkar, F. Z., (*EACTA*) A.28
Salak, N. *see* Germann, R. 357–362
Salazkin, I. *see* Troncy, E. 631–640
Salerno, L. *see* Ruschi, S., (*EACTA*) A.67
Salmela, L *see* McCourt, K. C., (*ARS*) 134P
Salvi, L., Mazzoni, M., Zucchetti, M., Juliano, G. and Sisillo, E. A method for cost containment in cardiac surgical ICU, (*EACTA*) A.95
Samarkandi, A. H. *see* Naguib, M. 450–455
Sammut, M. S. and Paes, M. L. Anaesthesia for laparoscopic cholecystectomy in a patient with Eisenmenger's syndrome 810–812
Sapsed-Byrne, S *see* Ma, D., (*ARS*) 141–142P
Sapsed-Byrne, S. M. *see* Lockwood, G. G. 517–520; 581–585; 586–589; Ma, D., (*ARS*) 686–687P
Sargentoni, J. *see* Lockwood, G. G. 581–585; 586–589
Sato, K. *see* Kikuchi, T. 128–130
Schachtrupp, A. *see* Weyland, A., (*EACTA*) A.53
Scheidegger, D. *see* Wu, X., (*EACTA*) A 48; (*EACTA*) A.49
Scherpereel, P. *see* Ausseur, A., (*EACTA*) A.74
Schlack, W., Preckel, B., Barthel, H., Obal, D. and Thamer, V. Halothane reduces reperfusion injury after regional ischaemia in the rabbit heart *in vivo* 88–96
Schlapp, U. *see* Hóche, A., (*EACTA*) A.24
Schmid, E. R. *see* Schmidlin, D., (*EACTA*) A.38
Schmidlin, D., Jenni, R. and Schmid, E. R. Transoesophageal echocardiography in cardiac and vascular surgery: therapeutic implications and inter-observer differences, (*EACTA*) A.38
Schmidt, M. *see* Buhre, W., (*EACTA*) A.4

Schmidt, W., Nottrott, M., Meineke, I., Schröder, T., Muller, S. and Hellige, G. Imipramine poisoning in an animal model-treatment with single cardiopulmonary bypass support or additional rein-haemoperfusion? (*EACTA*) A 64

Schnatmann, N. *see* Schwender, D. 53–58

Schoeffler, P. *see* Bazin, J. E., (*C*) 691

Scholz, J., Paris, A., von Knobelsdorff, G., Tonner, P. H. and Schulte am Esch, J. The effects of remifentanil on systemic and cerebral haemodynamics in patients undergoing cardiac surgery, (*EACTA*) A.7

Scholz, M. *see* Buhre, W. 311–316; Giannaris, S., (*EACTA*) A.23; Kazmaier, S., (*EACTA*) A.33; Spiegel, T.v., (*EACTA*) A.3; Wietasch, G., (*EACTA*) A.59

Schorn, B. *see* Buhre, W. 311–316; Giannaris, S., (*EACTA*) A.23; Kazmaier, S., (*EACTA*) A.88; Spiegel, T.v., (*EACTA*) A.3; Weyland, A., (*EACTA*) A.53

Schroder, T. *see* Schmidt, W., (*EACTA*) A.64

Schulte am Esch, J. *see* Scholz, J., (*EACTA*) A.7

Schuttler, J. *see* Dingemanse, J. 567–574

Schwall, B. *see* Frohlich, D. 289–292

Schwarz, B. *see* Germann, R. 357–362

Schweizer, A., Hón, L., Kalangos, A. and Licker, M. Effects of chronic angiotensin converting enzyme inhibition on renal function during cardiac surgery: the role of atrionatriuretic factor and prostanoids, (*EACTA*) A.16

Schweizer, A. *see* Vassalli, F., (*EACTA*) A.79

Schwender, D., Daunderer, M., Schnatmann, N., Klasing, S., Finsterer, U. and Peter, K. Midlatency auditory evoked potentials and motor signs of wakefulness during anaesthesia with midazolam 53–58

Schwilden, H. *see* Dingemanse, J. 567–574

Scott, R. C. *see* Golden, F. St C. 214–225

Sear, J. W ORG 21465, a new water-soluble steroid hypnotic: more of the same or something different? (*E*) 417–419

Seeberger, M. *see* Skarvan, K., (*EACTA*) A.39; Wu, X., (*EACTA*) A.48; (*EACTA*) A.49

Seeberger, M. D., Skarvan, K., Rosenthaler, C., Rohlfs, R., Dergeloo, O., Brett, W., Stulz, P. and Atar, D. Doppler monitoring of diastolic left ventricular function does not increase the sensitivity of dobutamine stress echocardiography for detecting inducible demand ischaemia in anaesthetized patients, (*EACTA*) A.40

Seitz, W. *see* Leuwer, M., (*ARS*) 132P

Senturk, M. *see* Tuğrul, E. 306–310

Seo, N. *see* Hirabayashi, Y. 563–566

Serpell, M. *see* Makin, A., (*ARS*) 687P

Serpell, M. G. *see* Hawksworth, C. R. E., (*ARS*) 674P

Shaaban, M. *see* Decoene, C., (*EACTA*) A.66

Shah, M. V. *see* O'Connor, P. J., (*EACTA*) A.31

Shannon, C. *see* Shinner, G., (*ARS*) 137–138P

Shapiro, A. *see* Olsfanger, D. 317–321

Sharpe, P. K. *see* Caleb, P., (*ARS*) 682P

Sharpe, R. M., Nathwani, D., Pal, S. K., Thornton, C., Brunner, M. D., Doré, C. J. and Newton, D. E. F. MAC values of mixtures, (*C*) 410–411

Sharpe, R. M. *see* Shinner, G., (*ARS*) 137–138P

Sharrock, N. E., Go, G., Williams-Russo, P., Haas, S. B. and Harpel, P. C. Comparison of extradural and general anaesthesia on the fibrinolytic response to total knee arthroplasty 29–34

Shearer, E. *see* MacKinnon, K. L., (*ARS*) 678P; Molnar, Z., (*ARS*) 678P

Sheridan, W. *see* Kuter, D. J., (*R*) 413

Shim, J. C. *see* Kim, K. S. 19–23

Shimizu, R. *see* Hirabayashi, Y. 563–566; Nakaigawa, Y. 363–368

Shimoda, O., Ikuta, Y., Isayama, S., Sakamoto, M. and Terasaki, H. Skin vasomotor reflex induced by laryngoscopy: comparison of the McCoy and Macintosh blades 714–718

Shinbori, H. *see* Kikuchi, T. 128–130

Shinner, G., Sharpe, R. M., Shannon, C., Thornton, C., Doré, C. J. and Brunner, M. D. Bolus doses of alfentanil prevent the increase in Pa amplitude associated with intubation in a dose-dependent manner, (*ARS*) 137–138P

Shirley, P. J. The future of ethical treatment, (*C*) 817

Shneerson, J. Cuff deflation for easier weaning from ventilation, (*C*) 145

Shorten, G. *see* Kussman, B. 122–124

Siegel, L. C. *see* Price Stover, E., (*EACTA*) A.70

Siegemund, M. *see* Wu, X., (*EACTA*) A.48; (*EACTA*) A.49

Signer, Ch. *see* Walpoth, B. H., (*EACTA*) A.37

Signorini, D. F. *see* Souter, M. J., (*E*) 420–421

Silvay, G. *see* Ammar, T., (*EACTA*) A.68

Sinclair, M. *see* Hwang, N. C., (*R*) 819–820

Singer, T. *see* Zollinger, A. 47–52

Sirinelli, A. *see* Lemoine, E., (*EACTA*) A.54

Sisillo, E. *see* Salvi, L., (*EACTA*) A.95

Sivalingham, P. *see* Hawksworth, C. R. E., (*ARS*) 139P

Sjoberg, F. *see* Bengtsson, M. 668–670

Skarvan, D. *see* Skarvan, K., (*EACTA*) A.39

Skarvan, K., Lintner, A., Skarvan, D. and Seeberger, M. Normal values for intraoperative left ventricular systolic and diastolic function as assessed by transoesophageal echocardiography, (*EACTA*) A.39

Skarvan, K. *see* Seeberger, M. D , (*EACTA*) A.40

Skinner, D., Swann, A., Peyton, R. and Roberts, C., (editors) *Cambridge Textbook of Accident and Emergency Medicine*, (*R*) 147

Skubas, N. J. *see* Bakola, A. A., (*EACTA*) A.44

Smit, A. J. *see* Girbes, A. R. J., (*C*) 263–264

Smith, G. Personal reflections, (*E*) 1–2

Smith, M. A. *see* Lockwood, G. G. 517–520

Smyrli, A. *see* Papadimitriou, L., (*EACTA*) A.51

Sneyd, J. R., Wright, P. M. C., Cross, M., Thompson, P., Voortman, G., Weideman, M. M., Andrews, C. J H. and Daniell, C. J. Administration to humans of ORG 21465, a water soluble steroid i.v. anaesthetic agent 427–432

Sneyd, J. R., Wright, P. M. C., Harris, D., Taylor, P. A., Vijn, P. C. M., Cross, M., Dale, H., Voortman, G. and Boen, P. Computer-controlled infusion of ORG 21465, a water soluble steroid i.v. anaesthetic agent, into human volunteers 433–439

Soeters, P. *see* Langenberg, C. J. M., (*EACTA*) A.50

Sonntag, H. *see* Buhre, W., (*EACTA*) A.4; 311–316, Kazmaier, S., (*EACTA*) A.33; (*EACTA*) A.88; Mielck, F., (*EACTA*) A.6; Weyland, A., (*EACTA*) A.53

Sorbara, C. *see* Pittarello, D., (*EACTA*) A.42

Soro, G. *see* Ranucci, M., (*EACTA*) A.84; (*EACTA*) A 85

Souter, M. J., Andrews, P. J. D., Piper, I. R. and Miller, J. D. Effects of alfentanil on cerebral haemodynamics in an experimental model of traumatic brain injury 97–102

Souter, M. J. and Signorini, D. F. Meta-analysis: greater than the sum of its parts? (*E*) 420–421

Spahn, D. R. *see* Zollinger, A. 47–52; (*C*) 816–817

Spence, A. A. *see* Thorpe, C. M. 402–409

Spiegel, T.v., Giannaris, S., Schorn, B., Scholz, M., Buhre, W. and Hoeft, A. Induction of anaesthesia with sufentanil is associated with blood volume redistribution, (*EACTA*) A.3

Spiegel, T.v. *see* Buhre, W., (*EACTA*) A.4

Spiliopoulos, A. *see* Vassalli, F., (*EACTA*) A.79

Spiss, C. *see* Hartmann, T. 482–487

Srinivasa, R., Morris, A., Enright, S. M. and Bellamy, M. C. Intravenous magnesium does not modify ischaemia–reperfusion syndrome in orthotopic liver transplantation, (*ARS*) 686P

Stahl, S. *see* Ben-David, B. 440–445

Stamford, J. A. *see* Bamigbade, T. A. 352–356

Stefani, M. *see* Ruschi, S., (*EACTA*) A.67

Stephan, H. *see* Mielck, F., (*EACTA*) A.6

Stevens, J. J. W. M. *see* Swart, M. L., (*ARS*) 677–678P

Stewart, J. I. M. *see* Hall, J. E. 285–288

Stieglitz, P. *see* Mezin, P. 327–331

Stienstra, R. *see* Veering, B. Th., (*C*) 144–145

Stoehr, S. *see* Zollinger, A. 47–52

Stott, S. *see* Cuthbertson, B. H., (*C*) 814

Striffeler, H. *see* Walpoth, B. H., (*EACTA*) A.37

Strunin, L. *see* Baskett, P. J. F., (*E*) 149–150

Studer, W. *see* Wu, X., (*EACTA*) A.48; (*EACTA*) A.49

Stulz, P. *see* Seeberger, M. D., (*EACTA*) A.40

Suzer, A., Suzer, Ö. and Aykaç, Z. Comparison of midazolam and propofol effects on cerebral metabolism during cardiopulmonary bypass, (*EACTA*) A.52

Suzer, A. *see* Suzer, Ö., (*EACTA*) A.1

Suzer, Ö., Erdogan, O., Diri, E., Süzer, A., Aykaç, Z. and Özuner, Z. Comparison of midazolam and thiopental on arrhythmias in ischaemia and reperfusion conditions in isolated perfused rat hearts, (*EACTA*) A.1

Süzer, Ö. *see* Suzer, A., (*EACTA*) A.52

Svedjeholm, R., Håkanson, E. and Szabo, Z. Predictors of atrial fibrillation in CABG surgery, (*EACTA*) A.83

Svedjeholm, R. *see* Szabo, Z., (*EACTA*) A.72

Svensén, C. *see* Hahn, R. G. 64–67

Swann, A. *see* Skinner, D., (*R*) 147

Swart, M. *see* Khan, O. A., (*ARS*) 675P; Taylor, S. R. J., (*ARS*) 674–675P

Swart, M. L., Stevens, J. J. W. M., Risdall, J. and Jones, J. G. Comparison of two steady state-auditory-evoked response methods for assessing depth of anaesthesia in routine clinical practice, (*ARS*) 677–678P

Swart, M. L. *see* Gupta, S., (*ARS*) 680P

Symington, M. J. *see* Loan, P. B., (*ARS*) 684P

Szabo, Z., Håkanson, E. and Svedjeholm, R. Influence of postoperative activated clotting time (ACT) on re-

operations for bleeding after cardiac surgery, (*EACTA*) A.72
Szabo, Z. *see* Svedjeholm, R., (*EACTA*) A.83
Szekely, A., Martin, K., Kilger, E., Vetter, H., Nollert, G., Janicke, U. and Conzen, P. Different influences of long-term ace inhibitor treatment for norepinephrine support during cardiac surgery, (*EACTA*) A.15

Taç, T., Yapýcý, N., Çoruh, T. and Aykaç, Z. Relations between the phosphodiesterase III inhibitors and cytokines in open heart surgery, (*EACTA*) A.25
Tagan, D. *see* Perret, C., (*R*) 266
Taivainen, T. *see* Meretoja, O. A., (*ARS*) 683–684P
Takeda, J. *see* Kiyama, S. 750–753
Talbot, J. *see* Groom, P., (*ARS*) 136P
Tanaka, H. *see* Fujii, Y. 539–540
Tanaka, K. *see* Hase, I. 740–743
Tanaka, Y. *see* Hirose, M. 120–121
Tarling, M. *see* Paris, S. T. 280–284
Taylor, P. A. *see* Sneyd, J R. 433–439
Taylor, R W. *see* Civetta, J. M., (*R*) 265
Taylor, R. W. *see* Kirby, R. R., (*R*) 147
Taylor, S. R. J., Khan, O. A., Swart, M. and Jones, J. G. Effects of low-dose isoflurane on contrast-sensitivity in volunteers, (*ARS*) 674–675P
Taylor, S. R. J. *see* Khan, O. A., (*ARS*) 675P
Tenling, A. *see* Magnusson, L., (*EACTA*) A.57
Terasaki, H. *see* Shimoda, O. 714–718
Ter Riet, P. M *see* Veering, B. Th., (*C*) 144–145
Thàmer, V. *see* Schlack, W. 88–96
Thelin, S. *see* Magnusson, L., (*EACTA*) A.57
Thompson, P. *see* Sneyd, J. R. 427–432
Thornton, C. *see* Sharpe, R. M., (*C*) 410–411; Shinner, G., (*ARS*) 137–138P
Thornton, J. *see* O'Beirne, H. A., (*ARS*) 132P
Thorpe, C. M. and Spence, A. A. Clinical evidence for delayed chloroform poisoning 402–409
Thum, P. *see* Leuwer, M., (*ARS*) 132P
Tibby, S. M. *see* Hatherill, M. 665–667
Tipton, M. J. *see* Golden, F. St C. 214–225
Tonner, P. H. *see* Scholz, J., (*EACTA*) A.7
Torrance, J. McK., Lewer, B. M. F. and Galletly, D. C. Interactions between mivacurium and prilocaine, (*C*) 262
Tournadre, J. P., Chassard, D. and Muchada, R. Overestimation of low cardiac output measured by thermodilution 514–516
Toyooka, H. *see* Fujii, Y. 539–540
Trinder, T. J. *see* Loan, P. B., (*ARS*) 684P
Troiani, R. *see* Ruschi, S., (*EACTA*) A.67
Tronc, F. *see* Aouifi, A., (*EACTA*) A.91
Troncy, E., Francœur, M., Salazkin, I., Yang, F., Charbonneau, M., Lesclerc, G., Vinay, P. and Blaise, G. Extra-pulmonary effects of inhaled nitric oxide in swine with and without phenylephrine 631–640
Tschanz, H. U. *see* Walpoth, B. H., (*EACTA*) A.30
Tuðrul, M. *see* Çamcý, E., (*EACTA*) A.58
Tuğrul, E., Čamci, E., Karadenİz, H., Senturk, M., Pembecİ, K. and Akpİr, K. Comparison of volume controlled with pressure controlled ventilation during one-lung anaesthesia 306–310
Tuovinen, K. *see* Nikanne, E. 606–608
Tupper-Carey, D. A., Walesby, R. K. and Feneck, R. O. Postoperative myocardial ischaemia and changes in indices of myocardial oxygen balance in patients undergoing CABG surgery, (*EACTA*) A.36
Tupper-Carey, D. A., Walesby, R. K., Newman, D. J., Price, C. P. and Feneck, R. O. An analysis of myocardial ischaemia and serial cardiac troponin I measurements in patients undergoing CABG surgery, (*EACTA*) A.29
Turkistani, A. *see* Naguib, M. 450–455
Tverskoy, M., Ben-Shlomo, I., Vainshtein, M., Zohar, S. and Fleyshman, G. Hypnotic effect of i.v. thiopentone is enhanced by i.m. administration of either lignocaine or bupivacaine 798–800
Tydén, H. *see* Magnusson, L., (*EACTA*) A.57

Ubags, L. H., Kalkman, C. J., Been, H. D. and Drummond, J. C. Differential effects of nitrous oxide and propofol on myogenic transcranial motor evoked responses during sufentanil anaesthesia 590–594
Uezono, S. *see* Goto, T. 595–599
Uphus, D. *see* Boldt, J. 733–739
Uppington, J. *see* Kussman, B. 122–124
Upton, R. N. and Ludbrook, G. L. A physiological model of induction of anaesthesia with propofol in sheep. 1. Structure and estimation of variables 497–504
Upton, R. N. *see* Ludbrook, G. L. 505–513
Urieta, A. *see* Laglera, S. 671–673

Vagnoni, S. *see* Zuccala, G. 776–781
Vainshtein, M. *see* Tverskoy, M. 798–800
Vakalos, A. *see* Lagonidis, D., (*EACTA*) A.46
Van Kleef, J. W. *see* Veering, B. Th., (*C*) 144–145
Van Nooten, G. *see* Foubert, L., (*EACTA*) A.90
Variushina, T. *see* Mizikov, V., (*EACTA*) A.73
Vassalli, F., Spiliopoulos, A., Höhn, L., De Perrot, M., Schweizer, A. and Licker, M. Perioperagive medical care of patients undergoing bilateral lung volume reduction for severe emphysema, (*EACTA*) A.79
Vaughan, R. S. *see* Koga, K., (*ARS*) 681P
Vedrinne, C. *see* Aouifi, A., (*EACTA*) A.91; (*EACTA*) A.93
Veering, B. Th., Ter Riet, P. M., Burm, A. G. L., Stienstra, R. and Van Kleef, J. W. Spinal anaesthesia. effect of the site of injection on the spread of analgesia, (*C*) 144–145
Venkatesh, B. Continuous intra-arterial blood-gas monitoring, (*C*) 815
Verborgh, C., Rombaut, A., D'haese, J., De Roover, E., Dupont, A. and Camu, F. Effects of R97399, a new PDE III inhibitor in patients with ischaemic heart disease, (*EACTA*) A.10
Verghese, C. *see* Bapat, P., (*C*) 145; Bapat, P. P., (*C*) 815; Brain, A. I. J. 699–703; 704–709; Kapila, A. 710–713
Vermeulen, P. M., Lerou, J. G. C., Dirksen, R., Booij, L. H. D. J. and Borm, G. F. Repeated enflurane anaesthetics and model predictions: a study of the variability in the predictive performance measures 488–496
Vetter, H. *see* Szekely, A., (*EACTA*) A.15
Vickers, M. D. *see* Couto da Silva, J. M. 103–112
Vijn, P. C. M. *see* Sneyd, J. R. 433–439
Vinay, P. *see* Troncy, E. 631–640
Vincent, J. L., (editor) *1997 Yearbook of Intensive Care and Emergency Medicine*, (*R*) 693
Vincent, R. Drugs in modern resuscitation 188–197
von Knobelsdorff, G. *see* Scholz, J., (*EACTA*) A.7
Voortman, G. *see* Sneyd, J. R. 427–432; 433–439
Vuk, Lj., Radojevic, D., Gradinac, S., Radomir, B , Jovic, M, Jovovic, Lj., Miric, M., Peric, M. and Bojic, M. Left ventricular remodelling (Battista procedure): early postoperative care, (*EACTA*) A.96
Vuylsteke, A., Callingham, B. C., Oduro, A. and Latimer, R. D. Comparison of clevidipine and nifedipine on isolated rat pulmonary artery and thoracic aorta, (*EACTA*) A.11
Vuylsteke, A. *see* Mur, D., (*EACTA*) A.92

Walden, F. M. Subclavian aneurysm causing brachial plexus injury after removal of a subclavian catheter 807–809
Walesby, R. K. *see* Tupper-Carey, D. A., (*EACTA*) A.29; (*EACTA*) A.36
Wallace, P. G. M. *see* Morton, N. S., (*R*) 267
Wallace, W. F. M. *see* McCaughey, W , (*R*) 820
Wallance, M. *see* Irving, G. A., (*R*) 265–266
Walling, P. T. Converting pH and H+, (*C*) 262–263
Walpoth, B. H., Auf der Maur, P., Fallegger, B., Striffeler, H., Baumgartner, I., Baumgartner, R., Signer, Ch., Althaus, U. and Kniemeyer, H. Quality control of carotid artery thrombendarterectomy by intraoperative transit time flow and resistance measurements, (*EACTA*) A.37
Walpoth, B. H., Celik, B., Carrel, T., Printzen, G , Tschanz, H. U., Althaus, U., Mohacsi, P., Reichenspurner, H. and Reitz, B. Assessment of troponin-T for detection of clinical rejection after cardiac transplantation, (*EACTA*) A.30
Walsh, T. S., Hopton, P. and Lee, A Comparison between reverse Fick and indirect calorimeter measurements of oxygen consumption in patients with fulminant hepatic failure, (*ARS*) 131–132P
Wang, C. *see* Ma, D. 525–529
Wang, M. and Russell, I. F. Absence of memory for intraoperative information, (*C*) 143
Wang, N. and Perryman, R. Cardiopulmonary bypass in a patient with Moyamoya disease, (*EACTA*) A.63
Wang, Y. *see* Kikuchi, T. 128–130
Wanzel, O. *see* La†nigg, A., (*EACTA*) A.21
Ward, J. E. H. *see* Wrench, I. J. 541–542
Warner, M. A. *see* Martin, J. T., (*R*) 693
Warren, P. M. *see* Foo, I. T. 41–46
Watson, I D. *see* MacKinnon, K. L., (*ARS*) 678P
Webster, N. R. *see* Bellamy, M. C. 338–341; Cuthbertson, B. H., (*C*) 814; Galley, H. F., (*ARS*) 678–679P
Weder, W. *see* Zollinger, A. 47–52
Weideman, M. M. *see* Sneyd, J. R. 427–432

Weimann, J., Hagenah, J. U. and Motsch, J. Reduction in nitrogen dioxide concentration by soda lime preparations during simulated nitric oxide inhalation 641–644
Welsh, K. R. *see* O'Connor, P. J., (*EACTA*) A.31
Welters, I., Menges, T., Knothe, C., Boldt, J. and Hempelmann, G. Thrombin generation and protein C activation in cardiac surgery patients, (*EACTA*) A.22
Welters, I., Menges, T., Zickmann, B., Knothe, C. and Hempelmann, G. Can albumin reduce platelet damage during extracorporeal circulation? (*EACTA*) A.71
Welters, I. *see* Ballesteros, M., (*EACTA*) A.19
Wenisch, C. *see* Bartunek, A., (*EACTA*) A.62
Wernberg, M. *see* Ilkjær, S. 600–605
Wernlund, J. *see* Magnusson, L., (*EACTA*) A.57
Wessels, J. A. *see* Miller, D. M., (*ARS*) 682–683P
West, S. P. *see* Curran, J. L., (*ARS*) 134P
Westerlind, A., Nilsson, F. and Ricksten, S.-E. The use of thoracic epidural analgesia after lung transplantation, (*EACTA*) A.82
Westerling, P. *see* McCrae, A. F. 558–562
Weyland, A., Schachtrupp, A., Kazmaier, S., Buhre, W., Schorn, B. and Sonntag, H. Cerebral haemodynamic effects of intra-aortic balloon counterpulsation, (*EACTA*) A.53
Weyland, A. *see* Buhre, W., (*EACTA*) A.4; 311–316; Giannaris, S., (*EACTA*) A.23; Kazmaier, S., (*EACTA*) A.33; (*EACTA*) A.88; Mielck, F., (*EACTA*) A.6; Wietasch, G., (*EACTA*) A.59
Wheatley, T J. Prophylaxis against deep vein thrombosis, (*C*) 146
White, S. A. *see* Goldhill, D. R., (*ARS*) 136P
Whitehead, C. F. and Baines, P. Use of inhaled nitric oxide in the critically ill, (*C*) 813–814
Whitwam, J. G. *see* Ma, D., (*ARS*) 141–142P; 525–529; (*ARS*) 686–687P
Wietasch, G., Bursch, J., Weyland, A., Scholz, M., Buhre, W. and Hoeft, A. Total blood volume, central blood volume, and extravascular lung water in children and adults, (*EACTA*) A.59
Wietasch, G. *see* Giannaris, S., (*EACTA*) A.23
Wildsmith, J. A. W. Interactions between mivacurium and prilocaine, (*C*) 262
Wildsmith, J. A. W. *see* Rae, S. M., (*E*) 271–273
Wilkes, A. R. and Mecklenburgh, J. S. Predicting the moisture-conserving performance of breathing system filters with different anaesthetic breathing systems, (*ARS*) 681–682P
Willard, T. *see* Nirmalan, M., (*ARS*) 135P
Williams, N. E. *see* Calvey, T. N., (*R*) 549
Williams-Russo, P. *see* Sharrock, N. E. 29–34
Wilson, C. M., Lillywhite, N., Wiltshire, S. and Mills, P. Buscopan does not improve pain after laparoscopic sterilization, (*ARS*) 139–140P
Wilson, J. A. *see* Lockwood, G. G. 581–585; 586–589
Wiltshire, S. *see* Wilson, C. M., (*ARS*) 139–140P
Winkelbauer, F. *see* Kellner, J., (*EACTA*) A.81
Wirtavuori, K. *see* Meretoja, O. A., (*ARS*) 683–684P
Wissler, R. N. *see* Richardson, M. G , (*C*) 261–262
Wojtalik, M. *see* Knapik, P., (*EACTA*) A.94
Wolf, H. J. *see* Germann, R. 357–362
Wrench, I. J., Cavill, G., Ward, J. E. H and Crossley, A. W. A. Comparison between alfentanil, pethidine and placebo in the treatment of post-anaesthetic shivering 541–542
Wright, P. M. C. *see* Sneyd, J. R. 427–432; 433–439
Wu, C.-P. *see* Huang, H.-H. 754–758
Wu, X., Studer, W., Siegemund, M., Seeberger, M. and Scheidegger, D. Reperfusion after supracoeliac aortic cross-clamping in a rat model: Effects of dopexamine on mesenteric oxygen transport, lactate flux and jejunal luminal PCO_2, (*EACTA*) A.49; Reperfusion after supracoeliac aortic cross-clamping in a rat model. effects of fluid-loading on mesenteric oxygen transport, lactate flux and jejunal luminal PCO_2, (*EACTA*) A.48

Yamato, R. *see* Nakaigawa, Y. 363–368
Yang, F. *see* Troncy, E. 631–640
Yapýcý, N. *see* Taç, T., (*EACTA*) A.25
Yate, P. M. *see* Paris, S. T. 280–284
Yavru, A. *see* Çamcý, E., (*EACTA*) A.58
Young, J. D. Inhaled nitric oxide in acute respiratory failure, (*E*) 695–696
Young, J. D., Rhodes, A. and Lamb, F. J. Inhaled nitric oxide, (*C*) 547
Young, J. D., Roberts, M. and Gale, L. B. Laboratory evaluation of the I-NOvent nitric oxide delivery device 398–401
Young, Y. *see* O'Beirne, H. A., (*ARS*) 132P

Zajchuk, R. and Grande, C. M., (editors) *Anesthesia and Perioperative Care of the Combat Casualty*, (*R*) 412–413
Zalunardo, M. P. *see* Zollinger, A. 47–52
Zell, M. *see* Dingemanse, J. 567–574
Zemgulis, V. *see* Magnusson, L., (*EACTA*) A.57
Zickmann, B. *see* Ballesteros, M., (*EACTA*) A.19; Welters, I., (*EACTA*) A.71
Zideman, D. A. Paediatric and neonatal life support 178–187
Zimpfer, M. *see* Hartmann, T. 482–487
Zohar, S. *see* Tverskoy, M. 798–800
Zollinger, A., Spahn, D. R. and Pasch, T. Continuous intra-arterial blood-gas monitoring, (*C*) 816–817
Zollinger, A., Spahn, D. R., Singer, T., Zalunardo, M. P., Stoehr, S., Weder, W. and Pasch, T. Accuracy and clinical performance of a continuous intra-arterial blood-gas monitoring system during thoracoscopic surgery 47–52
Zuccala, G., Pahor, M., Lattanzio, F., Vagnoni, S , Rodola, S., De Sole, P., Cittadini, A., Cocchi, A. and Bernabei, R. Detection of arrhythmogenic cellular magnesium depletion in hip surgery patients 776–781
Zucchetti, M. *see* Salvi, L., (*EACTA*) A.95
Zuker-Franklin, D. *see* Kuter, D. J., (*R*) 413

SUBJECT INDEX

1997 Yearbook of Intensive Care and Emergency Medicine, Vincent, J. L., (editor), (*R*) 693

Acid–base equilibrium, Drugs in modern resuscitation, Vincent, R. 188–197
Acid–base equilibrium, pH, Converting pH and H$^+$, Walling, P. T., (*C*) 262–263
——, Converting pH and H$^+$: a rule for the other thumb, Girling, D. K., (*C*) 410
——, Converting pH and H$^+$: a "rule of thumb", Burden, R. J., *et al.*, (*e*) 413
Advanced life support, Advanced life support guidelines, Robertson, C. E. 172–177
Age factors, Pharmacokinetic–pharmacodynamic modelling of the EEG effects of Ro 48-6791, a new short-acting benzodiazepine, in young and elderly subjects, Dingemanse, J., *et al.* 567–574
Airway, Management of the airway and ventilation during resuscitation, Gabbott, D. A., *et al.* 159–171
——, Management of the airway and ventilation during resuscitation, Richardson, C., (*C*) 814
Airway, complications, Aspects of resuscitation in trauma, Nolan, J. P., *et al.* 226–240
Allergy, Intradermal compared with prick testing in the diagnosis of anaesthetic allergy, Fisher, M. McD, *et al.* 59–63
Anaesthesia and Resuscitation, Jones, R. D. M., *et al.*, (editors), (*R*) 819
Anaesthesia, audit, Anaesthesia and the competence revolution, Greaves, J. D., (*E*) 555–557
——, Autotransfusion in major orthopaedic surgery: experience with 1785 patients, Borghi, B., *et al.* 662–664
——, *Meta-analysis*: greater than the sum of its parts? Souter, M. J., *et al.*, (*E*) 420–421
——, Preliminary survey into clinical attitudes to computer based decision support systems, Beatty, P. C. W., (*ARS*) 140–141P
——, Simulated anaesthetic emergencies, Byrne, A. J., *et al.*, (*C*) 690–691
——, Simulated anaesthetic emergencies, Gaba, D. M., *et al.*, (*C*) 689–690
——, Simulated anaesthetic emergencies, Kurrek, M., *et al.*, (*C*) 689
Anaesthesia, aviation, Catalogue of human error, Arnstein, F. 645–656
Anaesthesia, day-case, Comparison of perioperative ketoprofen 2.0 mg kg^{-1} with 0.5 mg kg^{-1} i.v. in small children during adenoidectomy, Nikanne, E., *et al.* 606–608
Anaesthesia, depth, Absence of memory for intraoperative information, Hooper, M. B., (*C*) 143
——, Absence of memory for intraoperative information, Wang, M., *et al.*, (*C*) 143
——, Comparison of two steady state-auditory-evoked response methods for assessing depth of anaesthesia in routine clinical practice, Swart, M. L., *et al.*, (*ARS*) 677–678P
——, Effect of extradural analgesia on the paradoxical arousal response of the electroencephalogram, Kiyama, S., *et al.* 750–753
——, Pharmacodynamics of thiopentone: nocifensive reflex threshold changes correlate with hippocampal electroencephalography, Archer, D. P., *et al.* 744–749
Anaesthesia, duration, Emergence times from xenon anaesthesia are independent of the duration of anaesthesia, Goto, T., *et al.* 595–599
Anaesthesia, general, Absence of memory for intraoperative information, Hooper, M. B., (*C*) 143
——, Absence of memory for intraoperative information, Wang, M., *et al.*, (*C*) 143
——, Anaesthesia for laparoscopic cholecystectomy in a patient with Eisenmenger's syndrome, Sammut, M. S., *et al.* 810–812
——, Comparison of extradural and general anaesthesia on the fibrinolytic response to total knee arthroplasty, Sharrock, N. E., *et al.* 29–34
——, Induction of anaesthesia with sufentanil is associated with blood volume redistribution, Spiegel, T.v., *et al.*, (*EACTA*) A.3
——, Time-frequency spectral analysis of heart rate variability during induction of general anaesthesia, Huang, H.-H., *et al.* 754–758
Anaesthesia, human error, Catalogue of human error, Arnstein, F. 645–656
Anaesthesia, journals, Personal reflections, Smith, G., (*E*) 1–2
Anaesthesia, obstetric, Comparison of single, end-holed and multi-orifice extradural catheters when used for continuous infusion of local anaesthetic during labour, Dickson, M. A. S., *et al.* 297–300
——, Effects of volume on spinal anaesthesia with 0.25% hyperbaric bupivacaine, King, H.-K., (*C*) 262
——, Extradural buprenorphine suppresses breast feeding after Caesarean section, Hirose, M., *et al.* 120–121
——, Outcome of labour using low-dose extradural bupivacaine compared with intramuscular pethidine, Robinson, P N., *et al.*, (*ARS*) 675–676P
——, Ropivacaine 0.75% for extradural anaesthesia in elective Caesarean section: an open clinical and pharmacokinetic study in mother and neonate, Morton, C. P. J., *et al.* 3–8
Anaesthesia, paediatric, Cardiovascular effects and time-course of action of cisatracurium in infants and children during thiopentone–alfentanil–nitrous oxide–oxygen anaesthesia, Meretoja, O. A., *et al.*, (*ARS*) 683–684P
——, Comparison of propofol and isoflurane ameliorating effects during rewarming period in paediatric cardiac surgery, Çamcý, E., *et al.*, (*EACTA*) A.58
——, Comparison of suxamethonium and different combinations of rocuronium and mivacurium for rapid tracheal intubation in children, Naguib, M., *et al* 450–455
——, Laryngeal mask airway and uncuffed trachael tubes are equally effective for low flow or closed system anaesthesia in children, Frohlich, D., *et al.* 289–292
——, Metabolic, biochemical and haemodynamic effects of infusion of propofol for long-term sedation of children undergoing intensive care, Martin, P. H., *et al.* 276–279
——, Obstruction of the lumen of a plastic 15-mm connector inserted into a cut paediatric tube—Is it possible to avoid this damage? Preis, C. A., *et al.*, (*C*) 692
——, Propofol in paediatric intensive care, Hatch, D. J., (*E*) 274–275
——, Rebound pulmonary vasoconstriction and desaturation on withdrawal of nitric oxide in infants after cardiac surgery, Knapik, P., *et al.*, (*EACTA*) A.94
——, Serum concentrations of bupivacaine during prolonged continuous paravertebral infusion in young infants, Cheung, S. L. W., *et al.* 9–13
——, Sevoflurane or halothane for paediatric endoscopy, Plowman, A., *et al.*, (*C*) 143–144
Anaesthetic Physiology and Pharmacology, McCaughey, W., *et al.*, (editors), (*R*) 820

Anaesthetic techniques, closed-system, Quantitative study of Lowe's square-root-of-time method of closed-system anaesthesia, Couto da Silva, J. M., *et al.* 103–112

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——, Sevoflurane or halothane for paediatric endoscopy, Plowman, A., *et al.*, (*C*) 143–144
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Anaesthetist, performance, Effect of music on the psychomotor performance of anaesthetists, Hawksworth, C. R. E., *et al.*, (*ARS*) 139P
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——, Pharmacokinetic and clinical study of ropivacaine and bupivacaine in women receiving extradural analgesia in labour, McCrae, A. F., *et al.* 558–562
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Analgesia, patient-controlled, Preoperative education reduces side effects when patient-controlled analgesia is used, Griffin, M J , *et al.*, (*ARS*) 138P
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Analgesics anti-inflammatory, steroid, Pain after laparoscopy, Alexander, J. I. 369–378
Analgesics non-opioid, ketoprofen, Comparison of perioperative ketoprofen 2 0 mg kg^{-1} with 0.5 mg kg^{-1} i.v. in small children during adenoidectomy, Nikanne, E., *et al.* 606–608
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Anatomy, extradural space, Magnetic resonance imaging of the extradural space of the thoracic spine, Hirabayashi, Y., *et al.* 563–566
Anesthesia and Perioperative Care of the Combat Casualty, Zajchuk, R., *et al.*, (editors), (*R*) 412–413
Antagonists opioid, naloxone, Naloxone inhibits gastric emptying but not gastrointestinal transit in the rat, Asai, T., *et al.*, (*ARS*) 133P
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Applied Cardiovascular Physiology. (*Update in Intensive Care*

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Basic life support, Basic life support, Handley, A. J. 151–158

Blood, Crystalloid vs. blood cardioplegia: a comparison of myocardial markers, Balogh, D., *et al.*, (*EACTA*) A.26

——, Plasma antifibrinolytic activity after injections of two dosages of tranexamic acid, Isetta, C., *et al.*, (*EACTA*) A.69

Blood, anticoagulants, aprotinin, A single dose of aprotinin or tranexamic acid in CPB priming reduces blood loss in primary cardiac surgery for coronary disease, Ruschi, S., *et al.*, (*EACTA*) A.67

——, Platelet effects of aprotinin and tranexamic acid, Ammar, T., *et al*, (*EACTA*) A.68

Blood, anticoagulants, heparin, Effects of preoperative i.v. heparin in coronary artery bypass grafting, Collard, E., *et al.*, (*EACTA*) A.65

Blood, anticoagulants, tranexamic acid, A single dose of aprotinin or tranexamic acid in CPB priming reduces blood loss in primary cardiac surgery for coronary disease, Ruschi, S., *et al.*, (*EACTA*) A.67

——, Platelet effects of aprotinin and tranexamic acid, Ammar, T., *et al.*, (*EACTA*) A.68

Blood, coagulation, Analysis of fibrinolysis during coronary artery surgery, Decoene, C., *et al.*, (*EACTA*) A.66

——, Comparison of extradural and general anaesthesia on the fibrinolytic response to total knee arthroplasty, Sharrock, N. E., *et al.* 29–34

——, Influence of postoperative activated clotting time (ACT) on re-operations for bleeding after cardiac surgery, Szabo, Z., *et al.*, (*EACTA*) A.72

——, Platelet function is inhibited by nitric oxide liberation during nitroglycerin-induced hypotension anaesthesia, Aoki, H., *et al.* 476–481

——, Thrombin generation and protein C activation in cardiac surgery patients, Welters, I., *et al.*, (*EACTA*) A.22

Blood, dynamics, Haemodynamic effects of celiprolol and sotalol after coronary artery bypass grafting, Foubert, L., *et al.*, (*EACTA*) A.90

——, Inhaled nitric oxide during anaesthesia for lung transplant, Della Rocca, G., *et al.*, (*EACTA*) A.77

Blood, flow, Blood flow and mivacurium-induced neuromuscular block at the orbicularis oculi and adductor pollicis muscles, Abdulatif, M., *et al.* 24–28

——, Cerebral haemodynamic effects of intra-aortic balloon counterpulsation, Weyland, A., *et al.*, (*EACTA*) A.53

——, Hepatic venous blood flow measured with retrograde thermodilution technique, Christiansen, C. L., *et al.*, (*EACTA*) A.55

——, Quality control of carotid artery thrombendarterectomy by intraoperative transit time flow and resistance measurements, Walpoth, B. H., *et al.*, (*EACTA*) A.37

——, Reperfusion after supracoeliac aortic cross-clamping in a rat model: Effects of dopexamine on mesenteric oxygen transport, lactate flux and jejunal luminal PCO_2, Wu, X., *et al.*, (*EACTA*) A.49

Blood, haemodilution, Acute normovolaemic haemodilution decreases postoperative allogeneic blood transfusion after total knee replacement, Olsfanger, D., *et al.* 317–321

——, Effect of haemoglobin concentration on brain oxygenation in focal stoke: a mathematical modelling study, Dexter, F., *et al.* 346–351

——, Plasma dilution and the rate of infusion of Ringer's solution, Hahn, R. G., *et al.* 64–67

Blood, haemodynamics, Awake or asleep pulmonary artery catheter insertion? A comparison of catecholamine and haemodynamic responses, O'Connor, P. J., *et al.*, (*EACTA*) A.31

——, Effects of fentanyl-midazolam anaesthesia on intrathoracic and total blood volume, Buhre, W , *et al.*, (*EACTA*) A.4

——, Effects of R97399, a new PDE III inhibitor in patients with ischaemic heart disease, Verborgh, C., *et al.*, (*EACTA*) A 10

——, Induction of anaesthesia with sufentanil is associated with blood volume redistribution, Spiegel, T v., *et al.*, (*EACTA*) A.3

——, Intravenous clonidine administration during CPB: effects on haemodynamic parameters and extubation time, Abay, G., *et al.*, (*EACTA*) A.8

——, The effects of remifentanil on systemic and cerebral haemodynamics in patients undergoing cardiac surgery, Scholz, J., *et al.*, (*EACTA*) A.7

Blood, haemoglobin, Effect of haemoglobin concentration on brain oxygenation in focal stoke: a mathematical modelling study, Dexter, F., *et al.* 346–351

Blood, haemolysis, Haemolysis after etomidate: comparison of propylene glycol and lipid formulations, Doenicke, A., *et al.* 386–388

Blood, haemoperfusion, Imipramine poisoning in an animal model-treatment with single cardiopulmonary bypass support or additional rein-haemoperfusion? Schmidt, W., *et al.*, (*EACTA*) A.64

Blood, loss, Influence of postoperative activated clotting time (ACT) on re-operations for bleeding after cardiac surgery, Szabo, Z., *et al.*, (*EACTA*) A 72

Blood, platelets, Can albumin reduce platelet damage during extracorporeal circulation? Welters, I , *et al.*, (*EACTA*) A.71

——, Platelet effects of aprotinin and tranexamic acid, Ammar, T., *et al.*, (*EACTA*) A.68

——, Platelet function is inhibited by nitric oxide liberation during nitroglycerin-induced hypotension anaesthesia, Aoki, H., *et al.* 476–481

Blood, salvage, Autotransfusion in major orthopaedic surgery· experience with 1785 patients, Borghi, B., *et al.* 662–664

Blood, transfusion, Acute normovolaemic haemodilution decreases postoperative allogeneic blood transfusion after total knee replacement, Olsfanger, D., *et al.* 317–321

——, Autotransfusion in major orthopaedic surgery: experience with 1785 patients, Borghi, B., *et al.* 662–664

Blood, volume, Effects of fentanyl-midazolam anaesthesia on intrathoracic and total blood volume, Buhre, W., *et al.*, (*EACTA*) A.4

——, Induction of anaesthesia with sufentanil is associated with blood volume redistribution, Spiegel, T.v., *et al.*, (*EACTA*) A.3

——, Total blood volume, central blood volume, and extravascular lung water in children and adults, Wietasch, G., *et al.*, (*EACTA*) A.59

Book Reviews

1997 Yearbook of Intensive Care and Emergency Medicine, Vincent, J. L., (editor), (*R*) 693

Anaesthesia and Resuscitation, Jones, R. D. M., *et al.*, (editors), (*R*) 819

Anaesthetic Physiology and Pharmacology, McCaughey, W., *et al.*, (editors), (*R*) 820

Anesthesia and Perioperative Care of the Combat Casualty, Zajchuk, R., *et al.*, (editors), (*R*) 412–413

Applied Cardiovascular Physiology. (Update in Intensive Care and Emergency Medicine Series), Pinsky, M R., (editor), (*R*) 549

Cambridge Textbook of Accident and Emergency Medicine, Skinner, D., *et al.*, (editors), (*R*) 147

Cardiac Anaesthesia: A Practical Handbook, Hwang, N. C., *et al.*, (*R*) 819–820

Clinical Anaesthesia, Gwinutt, C. L., (*R*) 412

Critical Care, 3rd Edn, Civetta, J. M., *et al.*, (editors), (*R*) 265

Critical Care Medicine: Perioperative Management, Murray, M., *et al.*, (editors), (*R*) 267

Essentials of Pediatric Intensive Care, 2nd Edn, Levin, D L., *et al.*, (editors), (*R*) 818–819

Handbook of Critical Care, 2nd Edn. Kirby, R. R., *et al.*, (editors), (*R*) 147

Hyperthermic and Hypermetabolic Disorders, Hopkins, P. M., *et al.*, (editors), (*R*) 266

Intensive Care Manual, 4th Edn, Oh, T. E., (editor), (*R*) 266–267

Book Reviews
Manual of Acute Pain Management in Children, McKenzie, I., *et al.*, (editors), (*R*) 819
Manual of Drug Interactions for Anesthesiology, 3rd Edn, Mueller, R. A., *et al.*, (*R*) 265
MCQs and OSCEs for the Primary FRCA, Doyle, E., *et al.*, (*R*) 818
Methods in Molecular Biology, volume 83: Receptor Signal Transduction Protocols, Challis, R. A. J., (editor), (*R*) 818
Pain Management for the Practising Physician, Irving, G. A., *et al.*, (*R*) 265–266
Positioning in Anesthesia and Surgery, 3rd Edn, Martin, J. T., *et al.*, (editors), (*R*) 693
Practical Anaesthesia and Analgesia for Day Surgery, Millar, J. M., *et al.*, (*R*) 818
Practical Obstetric Anesthesia, Dewan, D. M., *et al.*, (editors), (*R*) 147
Principles and Practice of Pharmacology for Anaesthetists, 3rd Edn, Calvey, T. N., *et al.*, (*R*) 549
Rapid Sequence Review of Anaesthesiology with Time-limited Pressure, Chee, W. K., (*R*) 820
Stabilisation and Transport of the Critically Ill, Morton, N. S., *et al.*, (editors), (*R*) 267
Textbook of Neuroanesthesia with Neurosurgical and Neuroscience Perspectives, Albin, M. S., (editor), (*R*) 412
The Pulmonary Artery Catheter in Critical Care—A Concise Handbook, Perret, C., *et al.*, (*R*) 266
The Pulmonary Circulation: Moving From Passive to Active Control, Pinsky, M. R., *et al.*, (editors), (*R*) 266
Thrombopoiesis and Thrombopoietins: Molecular, Cellular, Preclinical and Clinical Biology, Kuter, D. J., *et al.*, (editors), (*R*) 413
Brain, Cardiopulmonary bypass in a patient with Moyamoya disease, Wang, N., *et al.*, (*EACTA*) A.63
——, Cerebral haemodynamic effects of intra-aortic balloon counterpulsation, Weyland, A., *et al.*, (*EACTA*) A.53
——, Comparison of midazolam and propofol effects on cerebral metabolism during cardiopulmonary bypass, Suzer, A., *et al.*, (*EACTA*) A.52
——, Influence of sevoflurane on cerebral metabolism, blood flow and CO$_2$-reactivity, Mielck, F., *et al.*, (*EACTA*) A.6
——, Near-infrared spectroscopy for testing cerebral CO$_2$ reactivity, Kraus, B., *et al.*, (*EACTA*) A.34
——, Significance of regional cerebral oxygen saturation (rSO$_2$) during open heart surgery, Papadimitriou, L., *et al.*, (*EACTA*) A.51
——, The effects of remifentanil on systemic and cerebral haemodynamics in patients undergoing cardiac surgery, Scholz, J , *et al.*, (*EACTA*) A.7
Brain, anaesthesia, molecular effects, Halothane decreases K$^+$ evoked glutamate release from rat cerebrocortical slices, Nicol, B., *et al* , (*ARS*) 140P
Brain, autoregulation, Effect of 100% oxygen and 50% nitrous oxide on cerebral autoregulation as assessed by the transient hyperaemic response test, Girling, K. J., *et al.*, (*ARS*) 131P
Brain, blood flow, Effect of haemoglobin concentration on brain oxygenation in focal stoke: a mathematical modelling study, Dexter, F., *et al.* 346–351
——, Effect of incremental doses of sevoflurane on cerebral pressure autoregulation in humans, Gupta, S., *et al.* 469–472
——, Effects of alfentanil on cerebral haemodynamics in an experimental model of traumatic brain injury, Souter, M. J., *et al.* 97–102
Brain, cerebellum, Effects of volatile anaesthetics on spontaneous action potential firing of cerebellar Purkinje cells *in vitro* do not follow the Meyer–Overton rule, Antkowiak, B., *et al.* 617–624
Brain, cerebral cortex, Effects of ketamine and pentobarbitone on acetylcholine release from the rat frontal cortex *in vivo*, Kikuchi, T., *et al.* 128–130
Brain, convulsions, Effect of methohexitone and propofol with or without alfentanil on seizure duration and recovery in electroconvulsive therapy, Nguyen, T. T., *et al.* 801–803
Brain, evoked potentials, Differential effects of nitrous oxide and propofol on myogenic transcranial motor evoked responses during sufentanil anaesthesia, Ubags, L. H., *et al.* 590–594
——, MAC values of mixtures, Fassoulaki, A., (*C*) 410
——, MAC values of mixtures, Sharpe, R. M., *et al.*, (*C*) 410–411
——, Midlatency auditory evoked potentials and motor signs of wakefulness during anaesthesia with midazolam, Schwender, D., *et al.* 53–58
Brain, injury, Effects of alfentanil on cerebral haemodynamics in an experimental model of traumatic brain injury, Souter, M. J., *et al.* 97–102
Brain, intracranial pressure, Effects of alfentanil on cerebral haemodynamics in an experimental model of traumatic brain injury, Souter, M. J., *et al.* 97–102
Brain, ischaemia, Effect of haemoglobin concentration on brain oxygenation in focal stoke: a mathematical modelling study, Dexter, F., *et al.* 346–351
Brain, metabolism, Effect of haemoglobin concentration on brain oxygenation in focal stoke: a mathematical modelling study, Dexter, F., *et al.* 346–351
Brain, Purkinje neurones, Effects of volatile anaesthetics on spontaneous action potential firing of cerebellar Purkinje cells *in vitro* do not follow the Meyer–Overton rule, Antkowiak, B., *et al.* 617–624

Calcium channel block, clevidipine, Comparison of clevidipine and nifedipine onisolated rat pulmonary artery and thoracic aorta, Vuylsteke, A., *et al.*, (*EACTA*) A.11
——, Myocardial circulatory and metabolic effects of clevidipine after coronary artery bypass grafting (CABG), Kieler-Jensen, N., *et al.*, (*EACTA*) A.12
Calcium channel block, diltiazem, Evaluation of the effects of diltiazem on myocardial protection with troponin T in coronary artery bypass graft surgery, Aþkar, F. Z., *et al.*, (*EACTA*) A.28
Calcium channel block, felodipine, Effect of felodipine on renal function and vasoactive hormones in infrarenal aortic surgery, de Lasson, L., *et al.* 719–725
Calcium channel block, nicardipine, Effects of nicardipine on gastric mucosal perfusion during cardiopulmonary bypass, Lemoine, E., *et al.*, (*EACTA*) A.54
Cambridge Textbook of Accident and Emergency Medicine, Skinner, D.; *et al.*, (editors), (*R*) 147
Carbon dioxide, absorption, Partly exhausted soda lime or soda lime with water added, inhibits the increase in compound A concentration in the circle system during low-flow sevoflurane anaesthesia, Moriwaki, G., *et al.* 782–786
Carbon dioxide, measurement, Near-infrared spectroscopy for testing cerebral CO$_2$ reactivity, Kraus, B., *et al.*, (*EACTA*) A.34
Carbon dioxide, pneumoperitoneum, Pigs are not human, Lentschener, C., *et al.*, (*C*) 691–692
——, Pigs are not humans, Bazin, J. E., *et al.*, (*C*) 691
Cardiac Anaesthesia: A Practical Handbook, Hwang, N. C., *et al.*, (*R*) 819–820
Cardiorespiratory system, effects, Cardioventilatory coupling during anaesthesia, Galletly, D. C , *et al.* 35–40
——, Comparison of the effects of isoflurane with those of propofol on pulmonary vascular impedance in experimental embolic pulmonary hypertension, Ewalenko, P., *et al.* 625–630
Cardiovascular system, effects, Effects of magnesium sulphate on the cardiovascular system, coronary circulation and myocardial metabolism in anaesthetized dogs, Nakaigawa, Y., *et al.* 363–368
——, Pigs are not human, Lentschener, C., *et al.*, (*C*) 691–692
——, Pigs are not humans, Bazin, J. E., *et al.*, (*C*) 691
——, "Renal" dopamine, Girbes, A. R. J., *et al.*, (*C*) 263–264
——, "Renal" dopamine, Inglis, A., *et al.*, (*C*) 263
Cardiovascular system, responses, Changes in regulators of the circulation in patients undergoing lung surgery, Boldt, J., *et al.* 733–739
Cells, Effect of dexamethasone on oedema formation in patients undergoing coronary bypass surgery, Giannaris, S., *et al.*, (*EACTA*) A.23
——, Effects of dexamethasone on release of endotoxin and cytokines during hypothermic cardiopulmonary bypass, Hoche, A., *et al.*, (*EACTA*) A.24
——, Relations between the phosphodiesterase III inhibitors and cytokines in open heart surgery, Taç, T., *et al.*, (*EACTA*) A.25
——, The proinflammatory cytokine IL-8 is increased after intubation, La†nigg, A., *et al.*, (*EACTA*) A.21
——, Thrombin generation and protein C activation in cardiac surgery patients, Welters, I., *et al* , (*EACTA*) A.22
Children, Comparison of perioperative ketoprofen 2.0 mg kg^{-1} with 0.5 mg kg^{-1} i.v. in small children during adenoidectomy, Nikanne, E., *et al.* 606–608
——, Comparison of sevoflurane and halothane for outpatient dental anaesthesia in children, Paris, S. T., *et al.* 280–284
——, Continuous intra-arterial blood-gas monitoring in infants and children with cyanotic heart disease, Hatherill, M., *et al.* 665–667
——, Laryngeal mask airway and uncuffed trachael tubes are equally effective for low flow or closed system anaesthesia in children, Fröhlich, D., *et al.* 289–292
——, Paediatric and neonatal life support, Zideman, D. A. 178–187

Clinical Anaesthesia, Gwinutt, C. L., (*R*) 412
Complications, Normothermic perfusion: effects on postoperative multi-organ dysfunction, Ranucci, M., *et al.*, (*EACTA*) A 85
Complications, anaemia, Effect of haemoglobin concentration on brain oxygenation in focal stoke: a mathematical modelling study, Dexter, F., *et al.* 346–351
Complications, anaphylaxis, Intradermal compared with prick testing in the diagnosis of anaesthetic allergy, Fisher, M. McD, *et al.* 59–63
Complications, arrhythmia, Peri-arrest arrhythmias, Chamberlain, D. 198–202
Complications, asystole, Drugs in modern resuscitation, Vincent, R. 188–197
Complications, atelectasis, Efficacy of a vital capacity manœuvre to prevent post-cardiopulmonary bypass atelectasis: An experimental study, Magnusson, L., *et al.*, (*EACTA*) A.57
Complications, barotrauma, Anaesthesia for the surgery of emphysema, Conacher, I. D. 530–538
Complications, brachial plexus injury, Prognosis of intraoperative brachial plexus injury: a review of 22 cases, Ben-David, B., *et al.* 440–445
——, Subclavian aneurysm causing brachial plexus injury after removal of a subclavian catheter, Walden, F M. 807–809
Complications, cardiac arrest, Advanced life support guidelines, Robertson, C. E. 172–177
——, Aspects of resuscitation in trauma, Nolan, J. P., *et al.* 226–240
——, Basic life support, Handley, A. J. 151–158
——, Ethical aspects of resuscitation, Mohr, M., *et al.* 253–259
——, Fibrillation and defibrillation of the heart, Bossaert, L. L. 203–213
——, Management of the airway and ventilation during resuscitation, Gabbott, D. A., *et al.* 159–171
——, Management of the airway and ventilation during resuscitation, Richardson, C., (*C*) 814
——, Paediatric and neonatal life support, Zideman, D. A. 178–187
——, Peri-arrest arrhythmias, Chamberlain, D. 198–202
——, Resuscitation, Baskett, P. J. F., *et al.*, (*E*) 149–150
——, Uniform reporting in resuscitation, Dick, W. F. 241–252
Complications, convulsions, Enhanced choline acetyltransferase activity does not explain the action of inhaled convulsants, Griffiths, R., *et al.* 389–391
Complications, critical illness polyneuropathy, Predominant involvement of motor fibres in patients with critical illness polyneuropathy, Hund, E., (*C*) 548
——, Predominant involvement of motor fibres in patients with critical illness polyneuropathy, Latronico, N., *et al.*, (*C*) 547–548
Complications, deep vein thrombosis, Prophylaxis against deep vein thrombosis, Allsop, J. R., (*C*) 145
——, Prophylaxis against deep vein thrombosis, Wheatley, T. J., (*C*) 146
Complications, echinococcosis, A case of cardiac hydatidosis, Laglera, S., *et al.* 671–673
Complications, Eisenmenger's syndrome, Anaesthesia for laparoscopic cholecystectomy in a patient with Eisenmenger's syndrome, Sammut, M. S., *et al.* 810–812
Complications, emphysema, Anaesthesia for the surgery of emphysema, Conacher, I. D. 530–538
Complications, haemolysis, Haemolysis after etomidate: comparison of propylene glycol and lipid formulations, Doenicke, A., *et al.* 386–388
Complications, haemorrhage, Dopamine and intestinal mucosal tissue oxygenation in a porcine model of haemorrhage, Germann, R., *et al.* 357–362
Complications, head injury, Optimal brain tissue oxygenation during hyperventilation in patients with head injuries: measured by a mutliparameter sensor, Gupta, S., *et al.*, (*ARS*) 680P
Complications, humidification, Predicting the moisture-conserving performance of breathing system filters with different anaesthetic breathing systems, Wilkes, A. R., *et al.*, (*ARS*) 681–682P
Complications, hydatidosis, A case of cardiac hydatidosis, Laglera, S., *et al.* 671–673
Complications, hyperventilation, Optimal brain tissue oxygenation during hyperventilation in patients with head injuries: measured by a mutliparameter sensor, Gupta, S., *et al*, (*ARS*) 680P
Complications, hypoxia, Rebound pulmonary vasoconstriction and desaturation on withdrawal of nitric oxide in infants after cardiac surgery, Knapik, P., *et al.*, (*EACTA*) A.94
Complications, iron deficiency, Functional iron deficiency in orthotopic liver transplantation, Davey-Quinn, A., *et al.*, (*ARS*) 684–685P
Complications, magnesium depletion, Detection of arrhythmogenic cellular magnesium depletion in hip surgery patients, Zuccala, G., *et al.* 776–781
Complications, morbidity, Postoperative morbidity after coronary artery bypass graft surgery without cardiopulmonary bypass, Collard, E., *et al.*, (*EACTA*) A.86
Complications, Moyamoya disease, Cardiopulmonary bypass in a patient with Moyamoya disease, Wang, N , *et al.*, (*EACTA*) A 63
Complications, multi-system organ failure, *N*-acetylcysteine in multisystem organ failure, Molnar, Z., *et al.*, (*ARS*) 678P
Complications, muscular dystrophy, Dystrophin deficient *mdx* muscle is not prone to MH susceptibility: an *in vitro* study, Mader, N., *et al.* 125–127
Complications, neurological, Transient neurological symptoms after spinal anaesthesia with 4% mepivacaine and 0.5% bupivacaine, Hiller, A., *et al.* 301–305
Complications, obesity, Is severe obesity a risk factor for coronary surgery? Ranucci, M., *et al.*, (*EACTA*) A.84
Complications, oedema, Effect of dexamethasone on oedema formation in patients undergoing coronary bypass surgery, Giannaris, S., *et al.*, (*EACTA*) A.23
——, Lung transplant oedema. Clinical characteristics and radiological assessment? Kellner, J., *et al.*, (*EACTA*) A.81
——, Total blood volume, central blood volume, and extravascular lung water in children and adults, Wietasch, G., *et al.*, (*EACTA*) A.59
Complications, overdose, "Ecstacy" and the anaesthetist, Hall, A. P., (*E*) 697–698
Complications, palmar hyperhidrosis, Thorascopic sympathectomy, Fredman, B., *et al.*, (*C*) 688
——, Thorascopic sympathectomy, Parry-Jones, A. J. D., (*C*) 688
——, Thorascopic sympathectomy in the treatment of palmar hyperhidrosis: anaesthetic implications, Fredman, B., *et al.* 113–119
Complications, postoperative, Respiratory complications associated with tracheal intubation and extubation, Koga, K., *et al.*, (*ARS*) 681P
Complications, pulmonary hypertension, Results in five patients undergoing pulmonary thromboendarterectomy, Marcos, R. C., *et al.*, (*EACTA*) A.80
Complications, reoperation, Influence of postoperative activated clotting time (ACT) on re-operations for bleeding after cardiac surgery, Szabo, Z , *et al*, (*EACTA*) A.72
Complications, reperfusion syndrome, Intravenous magnesium does not modify ischaemia–reperfusion syndrome in orthotopic liver transplantation, Srinivasa, R., *et al.*, (*ARS*) 686P
Complications, seizures, Effect of methohexitone and propofol with or without alfentanil on seizure duration and recovery in electroconvulsive therapy, Nguyen, T. T., *et al.* 801–803
Complications, sepsis, Predominant involvement of motor fibres in patients with critical illness polyneuropathy, Hund, E., (*C*) 548
——, Predominant involvement of motor fibres in patients with critical illness polyneuropathy, Latronico, N., *et al.*, (*C*) 547–548
Complications, shivering, Comparison between alfentanil, pethidine and placebo in the treatment of post-anaesthetic shivering, Wrench, I. J., *et al.* 541–542
Complications, stenosis, Unsuspected difficult intubation caused by a laryngeal web, Chong, Z.-K., *et al.* 396–397
Complications, stress response, Clonidine and neuroendocrine stress response during lung surgery, Novak-Jankovič, V., *et al.*, (*EACTA*) A.9
Complications, subclavian aneurysm, Subclavian aneurysm causing brachial plexus injury after removal of a subclavian catheter, Walden, F. M. 807–809
Complications, thrombosis, Comparison of extradural and general anaesthesia on the fibrinolytic response to total knee arthroplasty, Sharrock, N. E., *et al.* 29–34
Complications, transient radicular irritation, Transient radicular irritation after spinal anaesthesia with 2% isobaric lignocaine, Ramasamy, D , *et al.* 394–395
Complications, trauma, Aspects of resuscitation in trauma, Nolan, J. P , *et al.* 226–240
Complications, ventricular fibrillation, Drugs in modern resuscitation, Vincent, R. 188–197
Computers, Preliminary survey into clinical attitudes to computer based decision support systems, Beatty, P. C. W., (*ARS*) 140–141P
——, The expanding role of simulators in risk management, Byrne, A. J., *et al.*, (*C*) 411
Critical Care, 3rd Edn, Civetta, J. M., *et al.*, (editors), (*R*) 265

Critical Care Medicine: Perioperative Management, Murray, M., *et al*, (editors), (*R*) 267

Dog, Dissociation between the effect of nitrous oxide on spontaneous and reflexly evoked sympathetic activity in dogs, Ma, D., *et al.* 525–529
——, Effects of magnesium sulphate on the cardiovascular system, coronary circulation and myocardial metabolism in anaesthetized dogs, Nakaigawa, Y., *et al.* 363–368
——, Overestimation of low cardiac output measured by thermodilution, Tournadre, J. P., *et al.* 514–516
Drowning, Immersion, near-drowining and drowning, Golden, F. St C., *et al.* 214–225

Embolism, pulmonary embolism, Comparison of the effects of isoflurane with those of propofol on pulmonary vascular impedance in experimental embolic pulmonary hypertension, Ewalenko, P., *et al.* 625–630
Enzymes, An analysis of myocardial ischaemia and serial cardiac troponin I measurements in patients undergoing CABG surgery, Tupper-Carey, D. A., *et al.*, (*EACTA*) A.29
——, Assessment of troponin-T for detection of clinical rejection after cardiac transplantation, Walpoth, B. H., *et al.*, (*EACTA*) A.30
——, Cardiac troponin I release using different myocardial management strategies, Barankay, A., *et al.*, (*EACTA*) A.27
——, Evaluation of the effects of diltiazem on myocardial protection with troponin T in coronary artery bypass graft surgery, Apkar, F. Z., *et al.*, (*EACTA*) A.28
Enzymes, choline acetyltransferase, Enhanced choline acetyltransferase activity does not explain the action of inhaled convulsants, Griffiths, R., *et al.* 389–391
Enzymes, cytochrome P450, I v. fentanyl decreases the clearance of midazolam, Hase, I., *et al.* 740–743
Enzymes, inhibition, Different influences of long-term ace inhibitor treatment for norepinephrine support during cardiac surgery, Szekely, A., *et al.*, (*EACTA*) A.15
——, Effects of chronic angiotensin converting enzyme inhibition on renal function during cardiac surgery: the role of atrionatriuretic factor and prostanoids, Schweizer, A., *et al.*, (*EACTA*) A.16
——, Haemodynamic response to angiotensin in patients treated with angiotensin converting enzyme inhibitors, Bennett, S. R., *et al.*, (*EACTA*) A.13
——, Plasma bradykinin during cardiopulmonary bypass and the effect of angiotensin converting enzyme inhibition, MacLaren, A. J., *et al.*, (*EACTA*) A.17
Enzymes, phosphodiesterase, inhibition, Effects of R97399, a new PDE III inhibitor in patients with ischaemic heart disease, Verborgh, C., *et al.*, (*EACTA*) A.10
Enzymes, proteinase, Thrombin generation and protein C activation in cardiac surgery patients, Welters, I., *et al.*, (*EACTA*) A.22
Equipment, Evaluation of two "universal" nitric oxide delivery systems, Mur, D., *et al.*, (*EACTA*) A.92
Equipment, alarms, Influence of pulse oximeter lower alarm limit on the incidence of hypoxaemia in the recovery room, Rheineck-Leyssius, A. T., *et al.* 460–464
Equipment, anaesthesia machines, Laryngeal mask airway and uncuffed trachael tubes are equally effective for low flow or closed system anaesthesia in children, Frohlich, D., *et al.* 289–292
Equipment, blood-gas monitors, Accuracy and clinical performance of a continuous intra-arterial blood-gas monitoring system during thoracoscopic surgery, Zollinger, A., *et al.* 47–52
——, Continuous intra-arterial blood-gas monitoring, Graystone, S. J., (*C*) 815–816
——, Continuous intra-arterial blood-gas monitoring, Venkatesh, B., (*C*) 815
——, Continuous intra-arterial blood-gas monitoring, Zollinger, A., *et al.*, (*C*) 816–817
Equipment, breathing systems, Estimation of cardiac output using the Maxima breathing system, Miller, D. M., *et al.*, (*ARS*) 682–683P
——, Laboratory evaluation of the I-NOvent nitric oxide delivery device, Young, J. D., *et al.* 398–401
——, Partly exhausted soda lime or soda lime with water added, inhibits the increase in compound A concentration in the circle system during low-flow sevoflurane anaesthesia, Moriwaki, G., *et al.* 782–786
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Equipment, catheters central venous, Subclavian aneurysm causing brachial plexus injury after removal of a subclavian catheter, Walden, F. M. 807–809
Equipment, catheters extradural, Comparison of single, end-holed and multi-orifice extradural catheters when used for continuous infusion of local anaesthetic during labour, Dickson, M. A. S., *et al.* 297–300
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Equipment, cuffs, tracheal, Lanz tube as alternative for ICU hyperbaric oxygen therapy, Molnar, Z., *et al.*, (*ARS*) 679–680P
Equipment, defibrillators, Fibrillation and defibrillation of the heart, Bossaert, L. L. 203–213
Equipment, filters, A survey of the practice of thoracic epidural analgesia in the United Kingdom, Romer, H. C., *et al.*, (*EACTA*) A.89
Equipment, gas analysers, Continuous intra-arterial blood-gas monitoring in infants and children with cyanotic heart disease, Hatherill, M., *et al.* 665–667
Equipment, heat-moisture exchangers, Predicting the moisture-conserving performance of breathing system filters with different anaesthetic breathing systems, Wilkes, A. R., *et al.*, (*ARS*) 681–682P
Equipment, laryngeal masks, The laryngeal mask for fibreoptic bronchoscopy in children, Mizikov, V., *et al.*, (*EACTA*) A.73
Equipment, masks anaesthesia, Laryngeal mask airway and uncuffed trachael tubes are equally effective for low flow or closed system anaesthesia in children, Frohlich, D., *et al.* 289–292
——, The intubating laryngeal mask airway: an initial assessment of performance, Kapila, A., *et al.* 710–713
——, The intubating laryngeal mask. I: development of a new device for intubation of the trachea, Brain, A. I. J., *et al.* 699–703
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Equipment, pulse oximeters, Influence of pulse oximeter lower alarm limit on the incidence of hypoxaemia in the recovery room, Rheineck-Leyssius, A. T., *et al.* 460–464
Equipment, scavenging devices, Inhaled nitric oxide, Young, J. D., *et al.*, (*C*) 547
——, Reduction in nitrogen dioxide concentration by soda lime preparations during simulated nitric oxide inhalation, Weimann, J., *et al.* 641–644
Equipment, tubes tracheal, Obstruction of the lumen of a plastic 15-mm connector inserted into a cut paediatric tube—Is it possible to avoid this damage? Preis, C. A., *et al.*, (*C*) 692
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——, Weaning: is the work of breathing via a tracheostomy tube similar to that via a tracheal tube? Bapat, P. P., *et al.*, (*C*) 815
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Equipment, tubes tracheostomy, Weaning: is the work of breathing via a tracheostomy tube similar to that via a tracheal tube? Bapat, P. P., *et al.*, (*C*) 815
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Equipment, valves, Improved intraoperative assessment of aortic stentless valves using transoeosophageal echocardiography, Morris, M. J., (*EACTA*) A.43
Equipment, warming blankets, Prevention of hypothermia by cutaneous warming with new electric blankets during abdominal surgery, Camus, Y., *et al.* 796–797
Equipment, warming devices, Heat retention using passive systems during anaesthesia: comparison of two plastic wraps, one with reflective properties, Deacock, S., *et al* 766–769
——, Thermal softening of tracheal tubes: an unrecognized hazard of the Bair Hugger active patient warming system, Ayala, J. L., *et al.* 543–545
Errata, Converting pH and H^+: a "rule of thumb", Burden, R. J., *et al.*, (*e*) 413
Essentials of Pediatric Intensive Care, 2nd Edn, Levin, D. L., *et al.*, (editors), (*R*) 818–819
Ethics, Ethical aspects of resuscitation, Mohr, M., *et al.* 253–259
——, The future of ethical treatment, Mohr, M., *et al.*, (*C*) 817
——, The future of ethical treatment, Shirley, P. J., (*C*) 817
Eye, intraocular pressure, Intraocular pressure and suxamethonium, Edmondson, L., (*C*) 146

Fluid balance, Plasma dilution and the rate of infusion of Ringer's solution, Hahn, R. G., *et al.* 64–67
Fluid therapy, Acute effect of mitral valve replacement on extravascular lung water in patients receiving colloid or crystalloid priming of cardiopulmonary bypass, Buhre, W., *et al.* 311–316
——, Aspects of resuscitation in trauma, Nolan, J. P., *et al.* 226–240
——, Plasma dilution and the rate of infusion of Ringer's solution, Hahn, R. G., *et al.* 64–67
Fluids, i.v., Plasma dilution and the rate of infusion of Ringer's solution, Hahn, R. G., *et al.* 64–67
Formulations, etomidate, Haemolysis after etomidate: comparison of propylene glycol and lipid formulations, Doenicke, A., *et al.* 386–388
Formulations, morphine, Pharmacokinetics of controlled release morphine (MST) in patients with liver cirrhosis, Kotb, H. I. M., *et al.* 804–806

Gases, non-anaesthetic, argon, Quantitative assessment of inhomogeneity of myocardial blood flow by a single breath inert gas technique. A model study, Kazmaier, S., *et al.*, (*EACTA*) A.33
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Gases non-anaesthetic, nitric oxide, Extra-pulmonary effects of inhaled nitric oxide in swine with and without phenylephrine, Troncy, E., *et al.* 631–640
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——, Use of inhaled nitric oxide in the critically ill, Cuthbertson, B. H., *et al.*, (*C*) 814
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Gases non-anaesthetic, nitrogen dioxide, Reduction in nitrogen dioxide concentration by soda lime preparations during simulated nitric oxide inhalation, Weimann, J., *et al.* 641–644
Gastrointestinal tract, Reperfusion after supracoeliac aortic cross-clamping in a rat model: Effects of dopexamine on mesenteric oxygen transport, lactate flux and jejunal luminal PCO_2, Wu, X., *et al.*, (*EACTA*) A.49
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Gastrointestinal tract, mucosal perfusion, Effects of nicardipine on gastric mucosal perfusion during cardiopulmonary bypass, Lemoine, E., *et al.*, (*EACTA*) A.54
——, Gut mucosal perfusion in infants undergoing cardiopulmonary bypass: effect of preoperative captopril, Booker, P. D., *et al.* 14–18
Genetic factors, hyperthermia, Detection of a novel mutation at amino acid position 614 in the ryanodine receptor in malignant hyperthermia, Quane, K. A., *et al.* 332–337
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Heart, antiarrhythmics, Drugs in modern resuscitation, Vincent, R. 188–197
Heart, arrhythmia, Changes in human coronary sinus blood flow and myocardial metabolism induced by ventricular fibrillation and defibrillation, Runsio, M., *et al.*, (*EACTA*) A.20
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——, Peri-arrest arrhythmias, Chamberlain, D 198–202
——, Predictors of atrial fibrillation in CABG surgery, Svedjeholm, R., *et al.*, (*EACTA*) A 83
Heart, arrhythmia, fibrillation, Fibrillation and defibrillation of the heart, Bossaert, L. L. 203–213
Heart, cardiac output, Comparison of the accuracy of the lithium dilution technique with the thermodilution technique for measurement of cardiac output, Kurita, T., *et al.* 770–775
——, Overestimation of low cardiac output measured by thermodilution, Tournadre, J. P., *et al.* 514–516
——, Pulse contour cardiac output measurement corresponds better with standard dilution technique than continuous thermodilution technique after hypothermic bypass, Bottiger, R. H., *et al.*, (*EACTA*) A.32
Heart, cardiopulmonary bypass, Acute effect of mitral valve replacement on extravascular lung water in patients receiving colloid or crystalloid priming of cardiopulmonary bypass, Buhre, W., *et al.* 311–316
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——, Effects of temperature on phrenic nerve and diaphragmatic function during cardiac surgery, Mills, G. H., *et al.* 726–732
——, Gut mucosal perfusion in infants undergoing cardiopulmonary bypass: effect of preoperative captopril, Booker, P. D., *et al.* 14–18
——, Immersion, near-drowining and drowning, Golden, F. St C., *et al.* 214–225
Heart, congenital defects, Continuous intra-arterial blood-gas monitoring in infants and children with cyanotic heart disease, Hatherill, M., *et al.* 665–667
Heart, contractility, Assessment of a new ventricular contractile index obtained with transoesophageal echocardiography before and after cardiopulmonary bypass in cardiac surgical patients, Kikura, M , *et al.* 759–765
Heart, defibrillators, Advanced life support guidelines, Robertson, C. E. 172–177
Heart, dobutamine, Perioperative transoesophageal echocardiography with low dose dobutamine: A feasible test for viability? Palmgren, I , *et al.*, (*EACTA*) A.41
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——, Time-frequency spectral analysis of heart rate variability during induction of general anaesthesia, Huang, H.-H., *et al.* 754–758
Heart, ischaemia, An analysis of myocardial ischaemia and serial cardiac troponin I measurements in patients undergoing CABG surgery, Tupper-Carey, D. A., *et al.*, (*EACTA*) A.29
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orthotopic heart transplantation? Bertolissi, M., *et al.*, (*EACTA*) A.60
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Heart, metabolism, Effects of magnesium sulphate on the cardiovascular system, coronary circulation and myocardial metabolism in anaesthetized dogs, Nakaigawa, Y., *et al.* 363–368
Heart, myocardial function, An experimental model of chronic myocardial hibernation in sheep, Raez, R., *et al.*, (*EACTA*) A.47
——, Beneficial effect of concomitant administration of isoflurane and nicorandil, Piriou, V., *et al.* 68–77
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——, Changes in human coronary sinus blood flow and myocardial metabolism induced by ventricular fibrillation and defibrillation, Runsio, M., *et al.*, (*EACTA*) A.20
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Heart, myocytes, Dose-dependent effects of halothane on contraction of rat ventricular myocytes, Davies, L. A., *et al.*, (*ARS*) 135P
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Heart, reperfusion injury, Halothane reduces reperfusion injury after regional ischaemia in the rabbit heart *in vivo*, Schlack, W., *et al* 88–96
Heart, resuscitation, Advanced life support guidelines, Robertson, C. E. 172–177
——, Aspects of resuscitation in trauma, Nolan, J. P., *et al.* 226–240
——, Basic life support, Handley, A. J. 151–158
——, Drugs in modern resuscitation, Vincent, R. 188–197
——, Ethical aspects of resuscitation, Mohr, M., *et al.* 253–259
——, Fibrillation and defibrillation of the heart, Bossaert, L. L. 203–213
——, Immersion, near-drowining and drowning, Golden, F. St C., *et al.* 214–225
——, Management of the airway and ventilation during resuscitation, Gabbott, D. A., *et al.* 159–171
——, Management of the airway and ventilation during resuscitation, Richardson, C., (*C*) 814
——, Paediatric and neonatal life support, Zideman, D. A. 178–187
——, Resuscitation, Baskett, P. J. F., *et al*, (*E*) 149–150
——, The future of ethical treatment, Mohr, M., *et al.*, (*C*) 817
——, The future of ethical treatment, Shirley, P. J., (*C*) 817
——, Uniform reporting in resuscitation, Dick, W. F. 241–252
Heart, transplantation, Assessment of troponin-T for detection of clinical rejection after cardiac transplantation, Walpoth, B. H., *et al.*, (*EACTA*) A.30
——, Impact of preoperative pulmonary vascular resistance and ischaemic time on the cardiovascular function after orthotopic heart transplantation, Bertolissi, M., *et al.*, (*EACTA*) A.61
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Heart, ventricles, Validity of acoustic quantification colour kinesis for detection of left ventricular regional wall motion abnormalites: a transoesophageal echocardiographic study, Hartmann, T., *et al* 482–487
History, anaesthesia, Clinical evidence for delayed chloroform poisoning, Thorpe, C. M., *et al.* 402–409
——, So just who was James "Young" Simpson? Rae, S. M., *et al.*, (*E*) 271–273
History, chloroform, Clinical evidence for delayed chloroform poisoning, Thorpe, C. M., *et al.* 402–409
History, Simpson, James Young, So just who was James "Young" Simpson? Rae, S. M., *et al*, (*E*) 271–273
Hormones, adrenal, Effects of a single dose of etomidate on adreno-cortical function in the critically ill, Absalom, A. R., *et al.*, (*ARS*) 679P
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Hyperthermia, Is there a difference in myofilament calcium sensitivity between malignant hyperthermia susceptible and normal skeletal muscle? Enright, S. M., *et al.*, (*ARS*) 685P
Hyperthermic and Hypermetabolic Disorders, Hopkins, P M., *et al.*, (editors), (*R*) 266
Hypnotics barbiturate, pentobarbitone, Effects of ketamine and pentobarbitone on acetylcholine release from the rat frontal cortex *in vivo*, Kikuchi, T., *et al.* 128–130
——, Effects of magnesium sulphate on the cardiovascular system, coronary circulation and myocardial metabolism in anaesthetized dogs, Nakaigawa, Y., *et al.* 363–368
Hypnotics barbiturates, thiopental, Comparison of midazolam and thiopental on arrhythmias in ischaemia and reperfusion conditions in isolated perfused rat hearts, Suzer, Ö, *et al.*, (*EACTA*) A.1
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——, Pharmacokinetics of midazolam given as an intranasal spray to adult surgical patients, Bjorkman, S., *et al.* 575–580
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Hypnotics benzodiazopines, midazolam, Comparison of midazolam and thiopental on arrhythmias in ischaemia and reperfusion conditions in isolated perfused rat hearts, Suzer, Ö., *et al.*, (*EACTA*) A.1
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Hypothermia, Immersion, near-drowining and drowning, Golden, F. St C., *et al.* 214–225
Hypoxaemia, Continuous intra-arterial blood-gas monitoring in infants and children with cyanotic heart disease, Hatherill, M., *et al.* 665–667

——, Influence of pulse oximeter lower alarm limit on the incidence of hypoxaemia in the recovery room, Rheineck-Leyssius, A. T., *et al.* 460–464

Immersion, Immersion, near-drowining and drowning, Golden, F. St C., *et al.* 214–225
Immune response, Changes in inflammatory mediators during orthotopic liver transplantation, Bellamy, M. C., *et al.* 338–341
Induction, anaesthesia, A physiological model of induction of anaesthesia with propofol in sheep. 1. Structure and estimation of variables, Upton, R. N., *et al.* 497–504
——, A physiological model of induction of anaesthesia with propofol in sheep. 2. Model analysis and implications for dose requirements, Ludbrook, G. L., *et al.* 505–513
Infants, Continuous intra-arterial blood-gas monitoring in infants and children with cyanotic heart disease, Hatherill, M., *et al.* 665–667
——, Paediatric and neonatal life support, Zideman, D. A. 178–187
——, Serum concentrations of bupivacaine during prolonged continuous paravertebral infusion in young infants, Cheung, S L. W., *et al.* 9–13
Infection, Antibiotic prophylaxis with cefodizime in patients with CABG-operations, Bartunek, A., *et al.*, (*EACTA*) A.62
Infection, parasitic, A case of cardiac hydatidosis, Laglera, S., *et al.* 671–673
Infection, sepsis, Use of microalbuminuria as an indicator for the development of sepsis and multiple system organ failure, MacKinnon, K. L., *et al.*, (*ARS*) 678P
Infection, spinal, Extradural catheter-related infections in patients with infected cutaneous wounds, Bengtsson, M., *et al.* 668–670
Intensive care, A method for cost containment in cardiac surgical ICU, Salvi, L., *et al.*, (*EACTA*) A.95
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——, Influence of ventilation modes on analgesic and sedative demand and pulmonary gas exchange in patients after CABG-surgery, Kazmaier, S., *et al.*, (*EACTA*) A.88
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——, Propofol in paediatric intensive care, Hatch, D. J , (*E*) 274–275
——, The use of thoracic epidural analgesia after lung transplantation, Westerlind, A., *et al.*, (*EACTA*) A.82
——, Transoesophageal echocardiography in the I.C.U. setting: luxury or necessity? Lagonidis, D., *et al.*, (*EACTA*) A.46
——, Use of inhaled nitric oxide in the critically ill, Cuthbertson, B. H., *et al.*, (*C*) 814
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Intensive Care Manual, 4th Edn, Oh, T. E , (editor), (*R*) 266–267
Intensive care, sedation, Metabolic, biochemical and haemodynamic effects of infusion of propofol for long-term sedation of children undergoing intensive care, Martin, P. H., *et al.* 276–279
Interactions drug, dexmedetomidine, Interactive effects of morphine and dexmedetomidine on gastrointestinal transit and gastric emptying in the rat, Asai, T , *et al.*, (*ARS*) 133P
Interactions drug, mivacurium, Comparison of suxamethonium and different combinations of rocuronium and mivacurium for rapid tracheal intubation in children, Naguib, M., *et al* 450–455
Interactions drug, morphine, Interactive effects of morphine and dexmedetomidine on gastrointestinal transit and gastric emptying in the rat, Asai, T., *et al.*, (*ARS*) 133P
Interactions drug, rocuronium, Comparison of suxamethonium and different combinations of rocuronium and mivacurium for rapid tracheal intubation in children, Naguib, M., *et al.* 450–455
Intubation tracheal, Bolus doses of alfentanil prevent the increase in Pa amplitude associated with intubation in a dose-dependent manner, Shinner, G., *et al.*, (*ARS*) 137–138P
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Intubation tracheal, difficult, Sevoflurane for difficult tracheal intubation, Mostafa, S. M., *et al.* 392–393
——, Unsuspected difficult intubation caused by a laryngeal web, Chong, Z.-K., *et al.* 396–397
Intubation tracheal, technique, Rapid tracheal intubation with propofol, alfentanil and a standard dose of vecuronium, Groener, R., *et al.* 384–385
——, The intubating laryngeal mask airway: an initial assessment of performance, Kapila, A., *et al.* 710–713
——, The intubating laryngeal mask. I: development of a new device for intubation of the trachea, Brain, A. I. J., *et al.* 699–703
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Intubation tracheal, training, Body posture during simulated tracheal intubation, Matthews, A. J., *et al.*, (*ARS*) 137P
Ions, calcium, Effect of halothane on K^+ and carbachol stimulated noradrenaline release and increased $_{i}$ in SH-SY5Y human neuroblastoma cells, Atcheson, R., *et al.* 78–83
——, Is there a difference in myofilament calcium sensitivity between malignant hyperthermia susceptible and normal skeletal muscle? Enright, S. M., *et al.*, (*ARS*) 685P
Ions, ion channels, Studies on the binding of amethocaine to rat cerebrocortical membranes, Kudo, T., *et al.* 521–524
Ions, ion channels, voltage-gated, Effect of halothane on K^+ and carbachol stimulated noradrenaline release and increased $_{i}$ in SH-SY5Y human neuroblastoma cells, Atcheson, R., *et al.* 78–83
Ions, magnesium, Administration of magnesium sulphate before rocuronium: effects on speed of onset and duration of neuromuscular block, Kussman, B., *et al.* 122–124
——, Detection of arrhythmogenic cellular magnesium depletion in hip surgery patients, Zuccala, G , *et al.* 776–781
——, Intravenous magnesium does not modify ischaemia–reperfusion syndrome in orthotopic liver transplantation, Srinivasa, R., *et al.*, (*ARS*) 686P

Kidney, blood flow, Effect of felodipine on renal function and vasoactive hormones in infrarenal aortic surgery, de Lasson, L., *et al.* 719–725
——, Low-dose dopamine: there is a scientific rationale, Gelman, S., (*C*) 546
Kidney, diuresis, Extra-pulmonary effects of inhaled nitric oxide in swine with and without phenylephrine, Troncy, E., *et al.* 631–640
Kidney, function, Effects of antiotensin on renal function in cardiac surgical patients, Bennett, S. R., *et al.*, (*EACTA*) A.18
——, Effects of chronic angiotensin converting enzyme inhibition on renal function during cardiac surgery: the role of atrionatriuretic factor and prostanoids, Schweizer, A., *et al.*, (*EACTA*) A.16
——, Extra-pulmonary effects of inhaled nitric oxide in swine with and without phenylephrine, Troncy, E., *et al.* 631–640
——, No direct effects of dopexamine on the isolated perfused rat kidney, Leuwer, M., *et al.*, (*ARS*) 132P
——, "Renal" dopamine, Girbes, A. R. J., *et al.*, (*C*) 263–264
——, "Renal" dopamine, Inglis, A., *et al.*, (*C*) 263

Larynx, damage, Unsuspected difficult intubation caused by a laryngeal web, Chong, Z.-K., *et al.* 396–397

Larynx, laryngoscopy, Skin vasomotor reflex induced by laryngoscopy: comparison of the McCoy and Macintosh blades, Shimoda, O., *et al* 714–718

——, Unsuspected difficult intubation caused by a laryngeal web, Chong, Z.-K., *et al.* 396–397

Liver, Hepatic venous blood flow measured with retrograde thermodilution technique, Christiansen, C. L., *et al.*, (*EACTA*) A.55

Liver, blood flow, Desflurane *vs* isoflurane in liver transplantation: a comparison of outcomes, O'Beirne, H. A., *et al.*, (*ARS*) 132P

Liver, cirrhosis, Pharmacokinetics of controlled release morphine (MST) in patients with liver cirrhosis, Kotb, H. I. M., *et al.* 804–806

Liver, transplantation, Changes in inflammatory mediators during orthotopic liver transplantation, Bellamy, M. C., *et al.* 338–341

——, Desflurane *vs* isoflurane in liver transplantation: a comparison of outcomes, O'Beirne, H. A., *et al.*, (*ARS*) 132P

——, Functional iron deficiency in orthotopic liver transplantation, Davey-Quinn, A., *et al.*, (*ARS*) 684–685P

Lung, Efficacy of a vital capacity manœuvre to prevent post-cardiopulmonary bypass atelectasis. An experimental study, Magnusson, L., *et al.*, (*EACTA*) A.57

Lung, adult respiratory distress syndrome, Oxygenation criteria—a plea for more information, Nielsen, M. S., *et al.*, (*C*) 260

——, Oxygenation criteria—a plea for more information, Peek, G. J., *et al.*, (*C*) 260

Lung, blood flow, Quantitative assessment of inhomogeneity of myocardial blood flow by a single breath inert gas technique. A model study, Kazmaier, S., *et al.*, (*EACTA*) A.33

——, Reperfusion after supracoeliac aortic cross-clamping in a rat model: effects of fluid-loading on mesenteric oxygen transport, lactate flux and jejunal luminal PCO_2, Wu, X., *et al.*, (*EACTA*) A.48

Lung, emphysema, Perioperagive medical care of patients undergoing bilateral lung volume reduction for severe emphysema, Vassalli, F., *et al.*, (*EACTA*) A.79

——, Perioperative management for lung volume reduction surgery for severe emphysema, Gressier, M., *et al.*, (*EACTA*) A.78

Lung, function, Comparison of the effects of isoflurane with those of propofol on pulmonary vascular impedance in experimental embolic pulmonary hypertension, Ewalenko, P., *et al.* 625–630

——, Effects of ventilation during cardiopulmonary bypass on pulmonary shunt, compliance and structure, Erhan, E., *et al.*, (*EACTA*) A.56

——, Inhaled nitric oxide in acute respiratory failure, Young, J. D., (*E*) 695–696

——, Postoperative respiratory dysfunction: is the site of surgery crucial? McKeague, H., *et al.*, (*E*) 415–416

——, Postoperative spirometry after laparoscopy for lower abdominal or upper abdominal surgical procedures, Joris, J., *et al.* 422–426

Lung, mucus, Comparison of isoflurane with propofol on respiratory cilia, Raphael, J. H., *et al.* 473–475

Lung, respiratory failure, Anaesthesia for the surgery of emphysema, Conacher, I. D. 530–538

Lung, trachea, Comparison of isoflurane with propofol on respiratory cilia, Raphael, J. H., *et al* 473–475

Lung, transplantation, Anaesthesia for the surgery of emphysema, Conacher, I. D. 530–538

Lung, vascular resistance, Impact of preoperative pulmonary vascular resistance and ischaemic time on the cardiovascular function after orthotopic heart transplantation, Bertolissi, M., *et al.*, (*EACTA*) A.61

Lung, volume, Anaesthesia for the surgery of emphysema, Conacher, I. D 530–538

Lung, water, Change in extravascular lung water after re-expansion of the collapsed lung in sheep measured by the thermo-saline dilution method, Nakatsuka, M., *et al.*, (*EACTA*) A.76

——, Total blood volume, central blood volume, and extravascular lung water in children and adults, Wietasch, G., *et al.*, (*EACTA*) A.59

Malignant hyperthermia, Detection of a novel mutation at amino acid position 614 in the ryanodine receptor in malignant hyperthermia, Quane, K A., *et al.* 332–337

——, Dystrophin deficient *mdx* muscle is not prone to MH susceptibility: an *in vitro* study, Mader, N., *et al.* 125–127

——, Genetic analysis reveals single recombinants in malignant hyperthermia, Curran, J. L , *et al.*, (*ARS*) 134P

——, Histological support for the difference between malignant hyperthermia susceptible (MHS), equivocal (MHE) and negative (MHN) muscle biopsies, Mezin, P., *et al.* 327–331

Manual of Acute Pain Management in Children, McKenzie, I , *et al.*, (editors), (*R*) 819

Manual of Drug Interactions for Anesthesiology, 3rd Edn, Mueller, R. A., *et al.*, (*R*) 265

MCQs and OSCEs for the Primary FRCA, Doyle, E , *et al.*, (*R*) 818

Measurement techniques, An analysis of myocardial ischaemia and serial cardiac troponin I measurements in patients undergoing CABG surgery, Tupper-Carey, D. A., *et al.*, (*EACTA*) A.29

——, Awake or asleep pulmonary artery catheter insertion? A comparison of catecholamine and haemodynamic responses, O'Connor, P. J., *et al.*, (*EACTA*) A.31

——, Cerebral haemodynamic effects of intra-aortic balloon counterpulsation, Weyland, A., *et al.*, (*EACTA*) A.53

——, Hepatic venous blood flow measured with retrograde thermodilution technique, Christiansen, C. L., *et al.*, (*EACTA*) A.55

——, Induction of anaesthesia with sufentanil is associated with blood volume redistribution, Spiegel, T.v., *et al.*, (*EACTA*) A.3

——, Postoperative myocardial ischaemia and changes in indices of myocardial oxygen balance in patients undergoing CABG surgery, Tupper-Carey, D. A., *et al.*, (*EACTA*) A.36

——, Pulse contour cardiac output measurement corresponds better with standard dilution technique than continuous thermodilution technique after hypothermic bypass, Bottiger, R. H., *et al.*, (*EACTA*) A.32

——, Quality control of carotid artery thrombendarterectomy by intraoperative transit time flow and resistance measurements, Walpoth, B. H., *et al.*, (*EACTA*) A.37

——, Quantitative assessment of inhomogeneity of myocardial blood flow by a single breath inert gas technique. A model study, Kazmaier, S., *et al.*, (*EACTA*) A.33

Measurement techniques, calorimetry, Comparison between reverse Fick and indirect calorimeter measurements of oxygen consumption in patients with fulminant hepatic failure, Walsh, T. S., *et al.*, (*ARS*) 131–132P

Measurement techniques, cardiac output, Comparison of the accuracy of the lithium dilution technique with the thermodilution technique for measurement of cardiac output, Kurita, T., *et al.* 770–775

——, Overestimation of low cardiac output measured by thermodilution, Tournadre, J. P., *et al.* 514–516

Measurement techniques, Doppler ultrasonography, Effect of incremental doses of sevoflurane on cerebral pressure autoregulation in humans, Gupta, S., *et al.* 469–472

Measurement techniques, electroencephalography, Does the insertion of earplugs affect the bispectral index of the sedated patient in the intensive care unit? Pearson, A. J., *et al.*, (*ARS*) 685–686P

Measurement techniques, Fick principle, Comparison between reverse Fick and indirect calorimeter measurements of oxygen consumption in patients with fulminant hepatic failure, Walsh, T. S., *et al.*, (*ARS*) 131–132P

Measurement techniques, flowmetry, Blood flow and mivacurium-induced neuromuscular block at the orbicularis oculi and adductor pollicis muscles, Abdulatif, M., *et al.* 24–28

——, Comparison of the accuracy of the lithium dilution technique with the thermodilution technique for measurement of cardiac output, Kurita, T., *et al.* 770–775

——, Gut mucosal perfusion in infants undergoing cardiopulmonary bypass: effect of preoperative captopril, Booker, P. D., *et al.* 14–18

——, Overestimation of low cardiac output measured by thermodilution, Tournadre, J. P., *et al.* 514–516

——, Skin vasomotor reflex induced by laryngoscopy: comparison of the McCoy and Macintosh blades, Shimoda, O., *et al.* 714–718

Measurement techniques, gas exchange, Accuracy and clinical performance of a continuous intra-arterial blood-gas monitoring system during thoracoscopic surgery, Zollinger, A., *et al.* 47–52

——, Continuous intra-arterial blood-gas monitoring, Graystone, S. J., (*C*) 815–816

——, Continuous intra-arterial blood-gas monitoring, Venkatesh, B , (*C*) 815

——, Continuous intra-arterial blood-gas monitoring, Zollinger, A., *et al.*, (*C*) 816–817

Measurement techniques, histology, Histological support for the difference between malignant hyperthermia susceptible (MHS), equivocal (MHE) and negative (MHN) muscle biopsies, Mezin, P., *et al.* 327–331

Measurement techniques, indication dilution, Acute effect of mitral valve replacement on extravascular lung water in patients receiving colloid or crystalloid priming of cardiopulmonary bypass, Buhre, W., *et al.* 311–316

Measurement techniques, lithium dilution, Comparison of the accuracy of the lithium dilution technique with the thermodilution technique for measurement of cardiac output, Kurita, T., *et al.* 770–775

Measurement techniques, magnetic resonance imaging, Magnetic resonance imaging of the extradural space of the thoracic spine, Hirabayashi, Y., *et al.* 563–566

Measurement techniques, magnetic resonance spectroscopy, Magnetic resonance spectroscopy of isoflurane kinetics in humans. Part I: elimination from the head, Lockwood, G. G., *et al.* 581–585

——, Magnetic resonance spectroscopy of isoflurane kinetics in humans. Part II: functional localization, Lockwood, G. G., *et al.* 586–589

Measurement techniques, microalbuminuria, Use of microalbuminuria as an indicator for the development of sepsis and multiple system organ failure, MacKinnon, K. L., *et al.*, (*ARS*) 678P

Measurement techniques, near-infrared spectroscopy, Near-infrared spectroscopy for testing cerebral CO_2 reactivity, Kraus, B., *et al.*, (*EACTA*) A.34

Measurement techniques, neural network, artificial, Artificial neural networks for distinguishing disturbed from undisturbed breathing, Caleb, P., *et al.*, (*ARS*) 682P

Measurement techniques, neuromuscular block, Comparison of neuromuscular blocking effects and train-of-four fade of cisatracurium with other blocking agents, Carroll, M. T., *et al.*, (*ARS*) 683P

Measurement techniques, spectral analysis, Time-frequency spectral analysis of heart rate variability during induction of general anaesthesia, Huang, H.-H., *et al.* 754–758

Measurement techniques, spectrophotometry, Detection of arrhythmogenic cellular magnesium depletion in hip surgery patients, Zuccala, G., *et al.* 776–781

Measurement techniques, thermodilution, Comparison of the accuracy of the lithium dilution technique with the thermodilution technique for measurement of cardiac output, Kurita, T., *et al.* 770–775

——, Overestimation of low cardiac output measured by thermodilution, Tournadre, J. P., *et al.* 514–516

Measurement techniques, tonometry, Gut mucosal perfusion in infants undergoing cardiopulmonary bypass: effect of preoperative captopril, Booker, P. D., *et al.* 14–18

Measurement techniques, transoesophageal Doppler, Overestimation of low cardiac output measured by thermodilution, Tournadre, J. P., *et al.* 514–516

Measurement techniques, transoesophageal echocardiography, Comparison of propofol-fentanyl and isoflurane-fentanyl anaesthesia with transoesophageal echocardiography for coronary artery bypass graft surgery, Nicolaides, A., *et al.*, (*EACTA*) A.45

——, Doppler monitoring of diastolic left ventricular function does not increase the sensitivity of dobutamine stress echocardiography for detecting inducible demand ischaemia in anaesthetized patients, Seeberger, M. D., *et al.*, (*EACTA*) A.40

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——, Improved intraoperative assessment of aortic stentless valves using transoeosophageal echocardiography, Morris, M. J., (*EACTA*) A.43

——, Normal values for intraoperative left ventricular systolic and diastolic function as assessed by transoesophageal echocardiography, Skarvan, K., *et al.*, (*EACTA*) A.39

——, Perioperative transoesophageal echocardiography with low dose dobutamine: A feasible test for viability? Palmgren, I., *et al.*, (*EACTA*) A.41

——, Transoesophageal echocardiography in cardiac and vascular surgery: therapeutic implications and inter-observer differences, Schmidlin, D., *et al.*, (*EACTA*) A.38

——, Transoesophageal echocardiography in the I.C.U. setting: luxury or necessity? Lagonidis, D., *et al.*, (*EACTA*) A.46

——, Transoesophageal echocardiography of mitral and pulmonary venous flow as estimation of diastolic function, Pittarello, D., *et al.*, (*EACTA*) A.42

——, Transoesophageal echocardiography of the right ventricle in thoracic patients, McMahon, C. C., *et al.*, (*EACTA*) A.75

Measurement techniques, ultrasound, Ultrasonographic measurement of gastric emptying in volunteers: assessment of technique and effect of low-dose dopamine, Goldhill, D. R., *et al.*, (*ARS*) 136P

Measurement techniques, voltammetry, Actions of tramadol, its enantiomers and principal metabolite, O-desmethyltramadol, on serotonin (5-HT) efflux and uptake in the rat dorsal raphe nucleus, Bamigbade, T. A., *et al* 352–356

Medico-legal, consent, Ethical aspects of resuscitation, Mohr, M., *et al.* 253–259

——, The future of ethical treatment, Mohr, M., *et al.*, (*C*) 817

——, The future of ethical treatment, Shirley, P. J., (*C*) 817

Memory, Absence of memory for intraoperative information, Hooper, M. B., (*C*) 143

——, Absence of memory for intraoperative information, Wang, M., *et al.*, (*C*) 143

Metabolism, Changes in human coronary sinus blood flow and myocardial metabolism induced by ventricular fibrillation and defibrillation, Runsio, M., *et al.*, (*EACTA*) A.20

——, Comparison of midazolam and propofol effects on cerebral metabolism during cardiopulmonary bypass, Suzer, A., *et al.*, (*EACTA*) A.52

——, Effect of intravascular volume load after induction of anaesthesia on oxygen consumption in cardiac surgery patients, Ballesteros, M., *et al.*, (*EACTA*) A.19

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Methods in Molecular Biology, volume 83: Receptor Signal Transduction Protocols, Challis, R. A. J., (editor), (*R*) 818

Model, burn injury, Effect of systemic N-methyl-D-aspartate receptor antagonist (dextromethorphan) on primary and secondary hyperalgesia in humans, Ilkjær, S., *et al.* 600–605

Model, computer simulation, Epiglottis modelling in a computer simulation of difficult laryngoscopy, Hawkins, M., *et al.*, (*ARS*) 136–137P

——, Simulated anaesthetic emergencies, Byrne, A J., *et al.*, (*C*) 690–691

——, Simulated anaesthetic emergencies, Gaba, D. M., *et al.*, (*C*) 689–690

——, Simulated anaesthetic emergencies, Kurrek, M., *et al.*, (*C*) 689

——, The expanding role of simulators in risk management, Byrne, A. J., *et al.*, (*C*) 411

Model, mathematical, Effect of haemoglobin concentration on brain oxygenation in focal stoke: a mathematical modelling study, Dexter, F., *et al.* 346–351

Model, mouse, Dystrophin deficient *mdx* muscle is not prone to MH susceptibility: an *in vitro* study, Mader, N., *et al.* 125–127

Model, neuroblastoma cells, Effect of halothane on K^+ and carbachol stimulated noradrenaline release and increased , in SH-SY5Y human neuroblastoma cells, Atcheson, R., *et al.* 78–83

Model, pharmacokinetic, Plasma dilution and the rate of infusion of Ringer's solution, Hahn, R G., *et al.* 64–67

Model, physiological, A physiological model of induction of anaesthesia with propofol in sheep. 1. Structure and estimation of variables, Upton, R. N., *et al.* 497–504

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——, Repeated enflurane anaesthetics and model predictions: a study of the variability in the predictive performance measures, Vermeulen, P. M., *et al.* 488–496

Model, pig, Efficacy of a vital capacity manœuvre to prevent post-cardiopulmonary bypass atelectasis: An experimental study, Magnusson, L., *et al.*, (*EACTA*) A.57

——, Pigs are not human, Lentschener, C., *et al.*, (*C*) 691–692

——, Pigs are not humans, Bazin, J. E., *et al.*, (*C*) 691

Model, rabbit, Halothane reduces reperfusion injury after regional ischaemia in the rabbit heart *in vivo*, Schlack, W , *et al.* 88–96

Model, rat, Actions of tramadol, its enantiomers and principal metabolite, O-desmethyltramadol, on serotonin (5-HT) efflux and uptake in the rat dorsal raphe nucleus, Bamigbade, T. A., *et al.* 352–356

——, Comparison of midazolam and thiopental on arrhythmias in ischaemia and reperfusion conditions in isolated perfused rat hearts, Suzer, Ö., *et al.*, (*EACTA*) A.1
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——, No direct effects of dopexamine on the isolated perfused rat kidney, Leuwer, M., *et al.*, (*ARS*) 132P
——, Opioid systems and the newborn, Marsh, D. F., *et al.* 787–795
——, Reperfusion after supracoeliac aortic cross-clamping in a rat model: Effects of dopexamine on mesenteric oxygen transport, lactate flux and jejunal luminal PCO_2, Wu, X., *et al.*, (*EACTA*) A.49
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——, Studies on the binding of amethocaine to rat cerebrocortical membranes, Kudo, T., *et al.* 521–524
Model, sheep, Change in extravascular lung water after re-expansion of the collapsed lung in sheep measured by the thermo-saline dilution method, Nakatsuka, M., *et al.*, (*EACTA*) A.76
——, Imipramine poisoning in an animal model-treatment with single cardiopulmonary bypass support or additional reinhaemoperfusion? Schmidt, W., *et al.*, (*EACTA*) A.64
Model, simulation, Accurate measurement of "true glottic view", Groom, P., *et al.*, (*ARS*) 680–681P
——, Modelling the photographic "restricted window" to derive "true glottic view", Groom, P., *et al.*, (*ARS*) 136P
Monitoring, Awake or asleep pulmonary artery catheter insertion? A comparison of catecholamine and haemodynamic responses, O'Connor, P. J., *et al.*, (*EACTA*) A.31
——, Echocardiographic and haemodynamic differences among patients undergoing the MAZE procedure, Bakola, A. A., *et al.*, (*EACTA*) A.44
——, Quality control of carotid artery thrombendarterectomy by intraoperative transit time flow and resistance measurements, Walpoth, B. H., *et al.*, (*EACTA*) A.37
Monitoring, blood gases, Continuous intra-arterial blood-gas monitoring in infants and children with cyanotic heart disease, Hatherill, M., *et al.* 665–667
——, Cutaneous blood gas monitoring during rigid bronchoscopy with high frequency Jet ventilation (HFJV), Ausseur, A., *et al.*, (*EACTA*) A.74
Monitoring, cardiac output, Estimation of cardiac output using the Maxima breathing system, Miller, D. M., *et al.*, (*ARS*) 682–683P
Monitoring, colour kinesis, Validity of acoustic quantification colour kinesis for detection of left ventricular regional wall motion abnormalites: a transoesophageal echocardiographic study, Hartmann, T., *et al.* 482–487
Monitoring, echocardiography, Validity of acoustic quantification colour kinesis for detection of left ventricular regional wall motion abnormalites: a transoesophageal echocardiographic study, Hartmann, T., *et al.* 482–487
Monitoring, electrocardiography, Cardioventilatory coupling during anaesthesia, Galletly, D. C., *et al.* 35–40
Monitoring, electroencephalography, Effect of extradural analgesia on the paradoxical arousal response of the electroencephalogram, Kiyama, S., *et al.* 750–753
——, Pharmacodynamics of thiopentone: nocifensive reflex threshold changes correlate with hippocampal electroencephalography, Archer, D. P., *et al.* 744–749
——, Pharmacokinetic–pharmacodynamic modelling of the EEG effects of Ro 48-6791, a new short-acting benzodiazepine, in young and elderly subjects, Dingemanse, J., *et al.* 567–574
Monitoring, evoked potentials, Bolus doses of alfentanil prevent the increase in Pa amplitude associated with intubation in a dose-dependent manner, Shinner, G., *et al.*, (*ARS*) 137–138P
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——, Midlatency auditory evoked potentials and motor signs of wakefulness during anaesthesia with midazolam, Schwender, D., *et al.* 53–58
Monitoring, neuromuscular function, Assessment of neuromuscular monitoring by intensive care nurses: comparison of the TOF-watch and tactile assessment, Greer, R., *et al.*, (*ARS*) 138–139P
Monitoring, temperature, Heat retention using passive systems during anaesthesia: comparison of two plastic wraps, one with reflective properties, Deacock, S., *et al.* 766–769
Monitoring, transoesophageal echocardiography, Assessment of a new ventricular contractile index obtained with transoesophageal echocardiography before and after cardiopulmonary bypass in cardiac surgical patients, Kikura, M., *et al.* 759–765
Monitoring, ventilation, Cardioventilatory coupling during anaesthesia, Galletly, D. C., *et al.* 35–40
Muscle skeletal, Blood flow and mivacurium-induced neuromuscular block at the orbicularis oculi and adductor pollicis muscles, Abdulatif, M., *et al.* 24–28
Muscle skeletal, blood flow, Blood flow and mivacurium-induced neuromuscular block at the orbicularis oculi and adductor pollicis muscles, Abdulatif, M., *et al.* 24–28
Muscle skeletal, diaphragm, Effects of temperature on phrenic nerve and diaphragmatic function during cardiac surgery, Mills, G. H., *et al.* 726–732
Muscle vascular, responses, Role of endothelium in the modulation of isoflurane-induced vasodilatation in rat thoracic aorta, Kirstetter, P., *et al.* 84–87
Muscles, skinned fibres, Is there a difference in myofilament calcium sensitivity between malignant hyperthermia susceptible and normal skeletal muscle? Enright, S. M., *et al.*, (*ARS*) 685P

Neonates, Opioid systems and the newborn, Marsh, D. F., *et al* 787–795
Nerve, damage (postoperative), Prognosis of intraoperative brachial plexus injury: a review of 22 cases, Ben-David, B., *et al.* 440–445
Nerve, neurotransmitters, Effects of ketamine and pentobarbitone on acetylcholine release from the rat frontal cortex *in vivo*, Kikuchi, T., *et al.* 128–130
——, Enhanced choline acetyltransferase activity does not explain the action of inhaled convulsants, Griffiths, R., *et al.* 389–391
Nerve, somatic, Dissociation between the effect of nitrous oxide on spontaneous and reflexly evoked sympathetic activity in dogs, Ma, D., *et al.* 525–529
Neuromuscular block, atracurium, Comparison of neuromuscular blocking effects and train-of-four fade of cisatracurium with other blocking agents, Carroll, M. T., *et al.*, (*ARS*) 683P
Neuromuscular block, cisatracurium, Cardiovascular effects and time-course of action of cisatracurium in infants and children during thiopentone–alfentanil–nitrous oxide–oxygen anaesthesia, Meretoja, O. A., *et al.*, (*ARS*) 683–684P
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Neuromuscular block, measurement of response, Administration of magnesium sulphate before rocuronium: effects on speed of onset and duration of neuromuscular block, Kussman, B., *et al.* 122–124
——, Assessment of neuromuscular monitoring by intensive care nurses: comparison of the TOF-watch and tactile assessment, Greer, R., *et al.*, (*ARS*) 138–139P
——, Blood flow and mivacurium-induced neuromuscular block at the orbicularis oculi and adductor pollicis muscles, Abdulatif, M., *et al.* 24–28
——, Interactions between mivacurium and pancuronium, Kim, K. S., *et al.* 19–23
——, Twitch augmentation and train-of-four fade during onset of neuromuscular block after subclinical doses of suxamethonium, Kim, S. Y., *et al.* 379–381
Neuromuscular block, mivacurium, Blood flow and mivacurium-induced neuromuscular block at the orbicularis oculi and adductor pollicis muscles, Abdulatif, M., *et al.* 24–28
——, Comparison of neuromuscular blocking effects and train-of-four fade of cisatracurium with other blocking agents, Carroll, M. T., *et al.*, (*ARS*) 683P
——, Comparison of suxamethonium and different combinations of rocuronium and mivacurium for rapid tracheal intubation in children, Naguib, M., *et al.* 450–455
——, Interactions between mivacurium and pancuronium, Kim, K. S., *et al* 19–23
——, Interactions between mivacurium and prilocaine, Torrance, J. McK., *et al.*, (*C*) 262
——, Interactions between mivacurium and prilocaine, Wildsmith, J. A. W., (*C*) 262
Neuromuscular block, pancuronium, Interactions between mivacurium and pancuronium, Kim, K. S., *et al.* 19–23
Neuromuscular block, rocuronium, Administration of magnesium sulphate before rocuronium: effects on speed of onset and duration of neuromuscular block, Kussman, B., *et al.* 122–124
——, Comparison of neuromuscular blocking effects and train-of-four fade of cisatracurium with other blocking agents, Carroll, M. T., *et al.*, (*ARS*) 683P
——, Comparison of rocuronium and suxamethonium for use

during rapid sequence induction of anaesthesia, McCourt, K C, *et al.*, (*ARS*) 134P
——, Comparison of suxamethonium and different combinations of rocuronium and mivacurium for rapid tracheal intubation in children, Naguib, M., *et al* 450–455
——, Spontaneous movements associated with rocuronium: is pain on injection the cause? Borgeat, A., *et al.* 382–383
Neuromuscular block, suxamethonium, Comparison of rocuronium and suxamethonium for use during rapid sequence induction of anaesthesia, McCourt, K C., *et al.*, (*ARS*) 134P
——, Comparison of suxamethonium and different combinations of rocuronium and mivacurium for rapid tracheal intubation in children, Naguib, M., *et al* 450–455
——, Intraocular pressure and suxamethonium, Edmondson, L., (*C*) 146
——, Twitch augmentation and train-of-four fade during onset of neuromuscular block after subclinical doses of suxamethonium, Kim, S. Y., *et al.* 379–381
Neuromuscular block, vecuronium, Comparison of neuromuscular blocking effects and train-of-four fade of cisatracurium with other blocking agents, Carroll, M. T., *et al*, (*ARS*) 683P
——, Effect of neuromuscular block using vecuronium on oxygen consumption in critically ill adults, Loan, P. B., *et al.*, (*ARS*) 684P
——, Rapid tracheal intubation with propofol, alfentanil and a standard dose of vecuronium, Groener, R., *et al.* 384–385
Neuromuscular relaxants, cisatracurium, Cisatracurium vs pancuronium for neuromuscular blockade in patients undergoing coronary revascularisation, Rauch, H., *et al.*, (*EACTA*) A.2
Neuromuscular relaxants, pancuronium, Cisatracurium vs pancuronium for neuromuscular blockade in patients undergoing coronary revascularisation, Rauch, H, *et al.*, (*EACTA*) A.2
Non-steroidal anti-inflammatory drugs, Pain after laparoscopy, Alexander, J I 369–378

Operating rooms, contamination, Environmental monitoring during gaseous induction with sevoflurane, Hall, J E, *et al.* 342–345
Oxygen, brain, Significance of regional cerebral oxygen saturation (rSO_2) during open heart surgery, Papadimitriou, L., *et al*, (*EACTA*) A.51
Oxygen, consumption, Comparison between reverse Fick and indirect calorimeter measurements of oxygen consumption in patients with fulminant hepatic failure, Walsh, T. S., *et al.*, (*ARS*) 131–132P
——, Effect of intravascular volume load after induction of anaesthesia on oxygen consumption in cardiac surgery patients, Ballesteros, M., *et al.*, (*EACTA*) A.19
——, Effect of neuromuscular block using vecuronium on oxygen consumption in critically ill adults, Loan, P. B., *et al.*, (*ARS*) 684P
——, Relationship between aortic cross clamp time and myocardial oxygen consumption during coronary artery bypass surgery (CABG), Langenberg, C. J M, *et al.*, (*EACTA*) A.50
Oxygen, delivery, Effect of neuromuscular block using vecuronium on oxygen consumption in critically ill adults, Loan, P. B., *et al.*, (*ARS*) 684P
Oxygen, gradients, Effect of assuming a fixed ($Ca_{O_2} - C\bar{v}_{O_2}$) on shunt calculations, Nirmalan, M., *et al.*, (*ARS*) 135P
Oxygen, saturation, Influence of pulse oximeter lower alarm limit on the incidence of hypoxaemia in the recovery room, Rheineck-Leyssius, A. T., *et al.* 460–464
Oxygen, therapy, Lanz tube as alternative for ICU hyperbaric oxygen therapy, Molnar, Z., *et al*, (*ARS*) 679–680P

Pain, chronic, Local anaesthetic agents inhibit $[^3H]$noradrenaline uptake into SH-SY5Y human neuroblastoma cells, Joyce, P. I., *et al*, (*ARS*) 677P
Pain, injection, Spontaneous movements associated with rocuronium: is pain on injection the cause? Borgeat, A., *et al.* 382–383
Pain Management for the Practising Physician, Irving, G. A, *et al*, (*R*) 265–266
Pain, measurement, Pre-emptive analgesia using local anaesthesia: a study in bilaterally symmetrical surgery, Campbell, W I., *et al.* 657–659
Pain, mechanism, Effect of systemic N-methyl-D-aspartate receptor antagonist (dextromethorphan) on primary and secondary hyperalgesia in humans, Ilkjær, S., *et al* 600–605
Pain, postoperative, Buscopan does not improve pain after laparoscopic sterilization, Wilson, C M., *et al.*, (*ARS*) 139–140P
——, Caudal tramadol for postoperative analgesia in paediatric hypospadias surgery, Prosser, D. P, *et al* 293–296
——, Does the addition of clonidine affect duration of analgesia of bupivacaine wound infiltration in inguinal hernia surgery? Elliott, S., *et al* 446–449
——, Effect of systemic N-methyl-D-aspartate receptor antagonist (dextromethorphan) on primary and secondary hyperalgesia in humans, Ilkjær, S., *et al* 600–605
——, Extradural buprenorphine suppresses breast feeding after Caesarean section, Hirose, M., *et al.* 120–121
——, Pain after laparoscopy, Alexander, J. I. 369–378
——, Pre-emptive analgesia using local anaesthesia: a study in bilaterally symmetrical surgery, Campbell, W. I., *et al.* 657–659
——, Preoperative education reduces side effects when patient-controlled analgesia is used, Griffin, M. J, *et al.*, (*ARS*) 138P
——, Serum concentrations of bupivacaine during prolonged continuous paravertebral infusion in young infants, Cheung, S. L. W., *et al* 9–13
Pharmacodynamics, A physiological model of induction of anaesthesia with propofol in sheep. 1 Structure and estimation of variables, Upton, R. N., *et al.* 497–504
——, A physiological model of induction of anaesthesia with propofol in sheep. 2. Model analysis and implications for dose requirements, Ludbrook, G. L, *et al.* 505–513
——, Comparison of neuromuscular blocking effects and train-of-four fade of cisatracurium with other blocking agents, Carroll, M. T., *et al.*, (*ARS*) 683P
——, Computer-controlled infusion of ORG 21465, a water soluble steroid i v. anaesthetic agent, into human volunteers, Sneyd, J. R., *et al.* 433–439
Pharmacodynamics, Ro 48-6791, Pharmacokinetic–pharmacodynamic modelling of the EEG effects of Ro 48-6791, a new short-acting benzodiazepine, in young and elderly subjects, Dingemanse, J., *et al.* 567–574
Pharmacodynamics, thiopentone, Pharmacodynamics of thiopentone: nocifensive reflex threshold changes correlate with hippocampal electroencephalography, Archer, D. P, *et al.* 744–749
Pharmacokinetics, bupivacaine, Pharmacokinetic and clinical study of ropivacaine and bupivacaine in women receiving extradural analgesia in labour, McCrae, A. F, *et al.* 558–562
Pharmacokinetics, fentanyl, I.v. fentanyl decreases the clearance of midazolam, Hase, I., *et al.* 740–743
Pharmacokinetics, isoflurane, Magnetic resonance spectroscopy of isoflurane kinetics in humans. Part I· elimination from the head, Lockwood, G. G, *et al* 581–585
——, Magnetic resonance spectroscopy of isoflurane kinetics in humans. Part II functional localization, Lockwood, G. G., *et al* 586–589
Pharmacokinetics, midazolam, I.v. fentanyl decreases the clearance of midazolam, Hase, I., *et al.* 740–743
——, Pharmacokinetics of midazolam given as an intranasal spray to adult surgical patients, Bjorkman, S, *et al* 575–580
Pharmacokinetics, models, Repeated enflurane anaesthetics and model predictions: a study of the variability in the predictive performance measures, Vermeulen, P. M., *et al.* 488–496
Pharmacokinetics, morphine, Pharmacokinetics of controlled release morphine (MST) in patients with liver cirrhosis, Kotb, H. I. M., *et al.* 804–806
Pharmacokinetics, ORG 21465, Administration to humans of ORG 21465, a water soluble steroid i.v anaesthetic agent, Sneyd, J. R., *et al.* 427–432
Pharmacokinetics, propofol, A physiological model of induction of anaesthesia with propofol in sheep 1 Structure and estimation of variables, Upton, R. N., *et al* 497–504
——, A physiological model of induction of anaesthesia with propofol in sheep. 2 Model analysis and implications for dose requirements, Ludbrook, G. L., *et al* 505–513
Pharmacokinetics, remifentanil, Effect of temperature and cardiopulmonary bypass on the pharmacokinetics of remifentanil, Russell, D., *et al.* 456–459
Pharmacokinetics, Ro 48-6791, Pharmacokinetic–pharmacodynamic modelling of the EEG effects of Ro 48-6791, a new short-acting benzodiazepine, in young and elderly subjects, Dingemanse, J., *et al.* 567–574
Pharmacokinetics, ropivacaine, Pharmacokinetic and clinical study of ropivacaine and bupivacaine in women receiving extradural analgesia in labour, McCrae, A. F., *et al.* 558–562
——, Ropivacaine 0.75 % for extradural anaesthesia in elective

Caesarean section. an open clinical and pharmacokinetic study in mother and neonate, Morton, C. P. J., *et al.* 3–8

——, Ropivacaine test dose in extradural anaesthesia, Dresner, M., *et al.*, (*C*) 813

——, Ropivacaine test dose in extradural anaesthesia, Morton, C. P. J., *et al.*, (*C*) 813

Pharmacology, buscopan, Buscopan does not improve pain after laparoscopic sterilization, Wilson, C. M., *et al.*, (*ARS*) 139–140P

Pharmacology, captopril, Gut mucosal perfusion in infants undergoing cardiopulmonary bypass: effect of preoperative captopril, Booker, P. D., *et al.* 14–18

Pharmacology, dextromethorphan, Effect of systemic N-methyl-D-aspartate receptor antagonist (dextromethorphan) on primary and secondary hyperalgesia in humans, Ilkjær, S., *et al.* 600–605

Pharmacology, domperidone, Effect of domperidone on the ventilatory response to transient hyperoxia in patients anaesthetized with isoflurane, Foo, I. T., *et al.* 41–46

Pharmacology, dopamine, Low-dose dopamine: there is a scientific rationale, Gelman, S., (*C*) 546

——, "Renal" dopamine, Girbes, A. R. J., *et al.*, (*C*) 263–264

——, "Renal" dopamine, Inglis, A., *et al.*, (*C*) 263

Pharmacology, "ecstacy", "Ecstacy" and the anaesthetist, Hall, A. P., (*E*) 697–698

Pharmacology, granisetron, Granisetron reduces the incidence of nausea and vomiting after middle ear surgery, Fujii, Y., *et al.* 539–540

Pharmacology, magnesium sulphate, Administration of magnesium sulphate before rocuronium: effects on speed of onset and duration of neuromuscular block, Kussman, B., *et al.* 122–124

——, Effects of magnesium sulphate on the cardiovascular system, coronary circulation and myocardial metabolism in anaesthetized dogs, Nakaigawa, Y., *et al.* 363–368

Pharmacology, *N*-acetylcysteine, *N*-acetylcysteine in multisystem organ failure, Molnar, Z., *et al.*, (*ARS*) 678P

Pharmacology, naloxone, Naloxone inhibits gastric emptying but not gastrointestinal transit in the rat, Asai, T., *et al.*, (*ARS*) 133P

Pharmacology, nicorandil, Beneficial effect of concomitant administration of isoflurane and nicorandil, Piriou, V., *et al.* 68–77

Pharmacology, niroglycerin, Platelet function is inhibited by nitric oxide liberation during nitroglycerin-induced hypotension anaesthesia, Aoki, H., *et al.* 476–481

Pharmacology, nitric oxide, Extra-pulmonary effects of inhaled nitric oxide in swine with and without phenylephrine, Troncy, E., *et al.* 631–640

——, Inhaled nitric oxide, Young, J. D., *et al.*, (*C*) 547

——, Inhaled nitric oxide in acute respiratory failure, Young, J. D., (*E*) 695–696

——, Laboratory evaluation of the I-NOvent nitric oxide delivery device, Young, J. D., *et al.* 398–401

——, Reduction in nitrogen dioxide concentration by soda lime preparations during simulated nitric oxide inhalation, Weimann, J., *et al.* 641–644

——, Role of endothelium in the modulation of isoflurane-induced vasodilatation in rat thoracic aorta, Kirstetter, P., *et al.* 84–87

——, Use of inhaled nitric oxide in the critically ill, Cuthbertson, B. H., *et al.*, (*C*) 814

——, Use of inhaled nitric oxide in the critically ill, Whitehead, C. F., *et al.*, (*C*) 813–814

Pharmacology, nitroglycerin, Extra-pulmonary effects of inhaled nitric oxide in swine with and without phenylephrine, Troncy, E., *et al.* 631–640

Pharmacology, ORG 21465, Administration to humans of ORG 21465, a water soluble steroid i.v. anaesthetic agent, Sneyd, J. R., *et al.* 427–432

——, Computer-controlled infusion of ORG 21465, a water soluble steroid i.v. anaesthetic agent, into human volunteers, Sneyd, J. R., *et al.* 433–439

——, ORG 21465, a new water-soluble steroid hypnotic: more of the same or something different? Sear, J. W., (*E*) 417–419

Pig, Comparison of the accuracy of the lithium dilution technique with the thermodilution technique for measurement of cardiac output, Kurita, T., *et al.* 770–775

——, Dopamine and intestinal mucosal tissue oxygenation in a porcine model of haemorrhage, Germann, R., *et al.* 357–362

——, Extra-pulmonary effects of inhaled nitric oxide in swine with and without phenylephrine, Troncy, E., *et al.* 631–640

Polypeptides, angiotensin, Effects of antiotensin on renal function in cardiac surgical patients, Bennett, S. R., *et al.*, (*EACTA*) A.18

——, Haemodynamic response to angiotensin in patients treated with angiotensin converting enzyme inhibitors, Bennett, S. R., *et al.*, (*EACTA*) A.13

Polypeptides, bradykinin, Plasma bradykinin during cardiopulmonary bypass and the effect of angiotensin converting enzyme inhibition, MacLaren, A. J., *et al.*, (*EACTA*) A.17

Polypeptides, cytokines, Changes in inflammatory mediators during orthotopic liver transplantation, Bellamy, M. C., *et al.* 338–341

——, Midazolam and propofol affect interleukin-8 release from human neutrophils at the post-translational level, Galley, H. F., *et al.*, (*ARS*) 678–679P

——, Relations between the phosphodiesterase III inhibitors and cytokines in open heart surgery, Taç, T., *et al.*, (*EACTA*) A.25

Polypeptides, cytokines, interleukin-8, The proinflammatory cytokine IL-8 is increased after intubation, La†nigg, A., *et al.*, (*EACTA*) A.21

Position, effects, Knee–chest *vs* horizontal side position during induction of spinal anaesthesia in patients undergoing lumbar disc surgery, Laakso, E., *et al.* 609–611

——, Lateral positioning for regional analgesia during labour, Kinsella, S. M., (*C*) 260–261

——, Lateral positioning for regional analgesia during labour, Richardson, M. G., *et al.*, (*C*) 261–262

Positioning in Ansthesia and Surgery, 3rd Edn, Martin, J. T., *et al.*, (editors), (*R*) 693

Potency, anaesthetic, ED_{50}, Interactions between mivacurium and pancuronium, Kim, K. S., *et al.* 19–23

Potency, anaesthetic, MAC, Does nitrous oxide antagonize sevoflurane-induced hypnosis? Katoh, T., *et al.* 465–468

——, MAC values of mixtures, Fassoulaki, A., (*C*) 410

——, MAC values of mixtures, Sharpe, R. M., *et al.*, (*C*) 410–411

Practical Anaesthesia and Analgesia for Day Surgery, Millar, J. M., *et al.*, (*R*) 818

Practical Obstetric Anesthesia, Dewan, D. M., *et al.*, (editors), (*R*) 147

Principles and Practice of Pharmacology for Anaesthetists, 3rd Edn, Calvey, T. N., *et al.*, (*R*) 549

Protein, Thrombin generation and protein C activation in cardiac surgery patients, Welters, I., *et al.*, (*EACTA*) A.22

Protein, albumin, Can albumin reduce platelet damage during extracorporeal circulation? Welters, I., *et al.*, (*EACTA*) A.71

Psychometric tests, Effects of low-dose isoflurane on contrast-sensitivity in volunteers, Taylor, S. R. J., *et al.*, (*ARS*) 674–675P

——, Effects of low-dose isoflurane on inhibition of saccadic eye movement, Khan, O. A., *et al.*, (*ARS*) 675P

Publications, *British Journal of Anaesthesia*, Personal reflections, Smith, G., (*E*) 1–2

Rabbit, Beneficial effect of concomitant administration of isoflurane and nicorandil, Piriou, V., *et al.* 68–77

——, Effect of sevoflurane on spontaneous sympathetic activity and baroreflexes in rabbits, Ma, D., *et al.*, (*ARS*) 141–142P

——, Halothane reduces reperfusion injury after regional ischaemia in the rabbit heart *in vivo*, Schlack, W., *et al.* 88–96

——, Synergistic effect of fentanyl and midazolam on phrenic nerve activity in rabbits, Ma, D., *et al.*, (*ARS*) 686–687P

Rapid Sequence Review of Anaesthesiology with Time-limited Pressure, Chee, W. K., (*R*) 820

Rat, Dose-dependent effects of halothane on contraction of rat ventricular myocytes, Davies, L. A., *et al.*, (*ARS*) 135P

——, Effects of alfentanil on cerebral haemodynamics in an experimental model of traumatic brain injury, Souter, M. J., *et al.* 97–102

——, Effects of ketamine and pentobarbitone on acetylcholine release from the rat frontal cortex *in vivo*, Kikuchi, T., *et al.* 128–130

——, Halothane decreases K^+ evoked glutamate release from rat cerebrocortical slices, Nicol, B., *et al.*, (*ARS*) 140P

——, No direct effects of dopexamine on the isolated perfused rat kidney, Leuwer, M., *et al.*, (*ARS*) 132P

——, Pharmacodynamics of thiopentone: nocifensive reflex threshold changes correlate with hippocampal electroencephalography, Archer, D. P., *et al.* 744–749

——, Role of endothelium in the modulation of isoflurane-induced vasodilatation in rat thoracic aorta, Kirstetter, P., *et al.* 84–87

Receptors, baroceptors, Effect of sevoflurane on spontaneous sympathetic activity and baroreflexes in rabbits, Ma, D., *et al.*, (*ARS*) 141–142P

Receptors, opioid, Effects of ketamine on cAMP formation in Chinese hamster ovary cells expressing recombinant opioid receptors, Hirota, K., *et al.*, (*ARS*) 141P
Receptors, ryanodine, Detection of a novel mutation at amino acid position 614 in the ryanodine receptor in malignant hyperthermia, Quane, K. A., *et al.* 332–337
Records, Utstein template, Uniform reporting in resuscitation, Dick, W. F. 241–252
Recovery, Effects of low-dose isoflurane on contrast-sensitivity in volunteers, Taylor, S. R. J., *et al.*, (*ARS*) 674–675P
——, Effects of low-dose isoflurane on inhibition of saccadic eye movement, Khan, O. A., *et al.*, (*ARS*) 675P
Recovery, postoperative, Emergence times from xenon anaesthesia are independent of the duration of anaesthesia, Goto, T., *et al.* 595–599
Reflexes, chemoreceptors, Effect of domperidone on the ventilatory response to transient hyperoxia in patients anaesthetized with isoflurane, Foo, I. T., *et al.* 41–46
Reflexes, sympathetic, Dissociation between the effect of nitrous oxide on spontaneous and reflexly evoked sympathetic activity in dogs, Ma, D., *et al.* 525–529

Sedation, Administration to humans of ORG 21465, a water soluble steroid i.v anaesthetic agent, Sneyd, J. R., *et al.* 427–432
——, Computer-controlled infusion of ORG 21465, a water soluble steroid i.v. anaesthetic agent, into human volunteers, Sneyd, J. R., *et al* 433–439
——, Metabolic, biochemical and haemodynamic effects of infusion of propofol for long-term sedation of children undergoing intensive care, Martin, P. H., *et al.* 276–279
——, ORG 21465, a new water-soluble steroid hypnotic: more of the same or something different? Sear, J W., (*E*) 417–419
——, Propofol in paediatric intensive care, Hatch, D J., (*E*) 274–275
Serotonin (5-hydroxytryptamine), Actions of tramadol, its enantiomers and principal metabolite, O-desmethyltramadol, on serotonin (5-HT) efflux and uptake in the rat dorsal raphe nucleus, Bamigbade, T. A., *et al* 352–356
Sheep, A physiological model of induction of anaesthesia with propofol in sheep. 1. Structure and estimation of variables, Upton, R N., *et al.* 497–504
——, A physiological model of induction of anaesthesia with propofol in sheep. 2 Model analysis and implications for dose requirements, Ludbrook, G. L., *et al.* 505–513
——, An experimental model of chronic myocardial hibernation in sheep, Raez, R., *et al.*, (*EACTA*) A.47
Skin, blood flow, Skin vasomotor reflex induced by laryngoscopy: comparison of the McCoy and Macintosh blades, Shimoda, O , *et al.* 714–718
Skin, tests, Intradermal compared with prick testing in the diagnosis of anaesthetic allergy, Fisher, M. McD, *et al* 59–63
Solubility, temperature, Effect of temperature on the solubility of desflurane, sevoflurane, enflurane and halothane in blood, Lockwood, G. G , *et al.* 517–520
Spinal cord, evoked potentials, Differential effects of nitrous oxide and propofol on myogenic transcranial motor evoked responses during sufentanil anaesthesia, Ubags, L. H., *et al.* 590–594
Stabilisation and Transport of the Critically Ill, Morton, N. S., *et al*, (editors), (*R*) 267
Statistics, meta-analysis, Meta-analysis: greater than the sum of its parts? Souter, M. J., *et al.*, (*E*) 420–421
Surgery, abdominal, Prevention of hypothermia by cutaneous warming with new electric blankets during abdominal surgery, Camus, Y., *et al.* 796–797
Surgery, cardiovascular, A method for cost containment in cardiac surgical ICU, Salvi, L., *et al*, (*EACTA*) A.95
——, A single dose of aprotinin or tranexamic acid in CPB priming reduces blood loss in primary cardiac surgery for coronary disease, Ruschi, S., *et al.*, (*EACTA*) A.67
——, Acute effect of mitral valve replacement on extravascular lung water in patients receiving colloid or crystalloid priming of cardiopulmonary bypass, Buhre, W., *et al.* 311–316
——, Analysis of fibrinolysis during coronary artery surgery, Decoene, C., *et al.*, (*EACTA*) A.66
——, Antibiotic prophylaxis with cefodizime in patients with CABG-operations, Bartunek, A., *et al.*, (*EACTA*) A.62
——, Arterial switch for transposition of great arteries anaesthesia & postoperative care, Aouifi, A., *et al.*, (*EACTA*) A.91
——, Assessment of a new ventricular contractile index obtained with transoesophageal echocardiography before and after cardiopulmonary bypass in cardiac surgical patients, Kikura, M., *et al.* 759–765
——, Awake or asleep pulmonary artery catheter insertion? A comparison of catecholamine and haemodynamic responses, O'Connor, P. J., *et al.*, (*EACTA*) A 31
——, Can albumin reduce platelet damage during extracorporeal circulation? Welters, I., *et al.*, (*EACTA*) A.71
——, Cardiac troponin I release using different myocardial management strategies, Barankay, A., *et al.*, (*EACTA*) A.27
——, Cardiopulmonary bypass in a patient with Moyamoya disease, Wang, N., *et al.*, (*EACTA*) A.63
——, Comparison of midazolam and propofol effects on cerebral metabolism during cardiopulmonary bypass, Suzer, A., *et al.*, (*EACTA*) A.52
——, Comparison of propofol and isoflurane ameliorating effects during rewarming period in paediatric cardiac surgery, Çamcý, E., *et al.*, (*EACTA*) A.58
——, Comparison of propofol-fentanyl and isoflurane-fentanyl anaesthesia with transoesophageal echocardiography for coronary artery bypass graft surgery, Nicolaides, A., *et al.*, (*EACTA*) A.45
——, Crystalloid vs. blood cardioplegia. a comparison of myocardial markers, Balogh, D., *et al.*, (*EACTA*) A.26
——, Different influences of long-term ace inhibitor treatment for norepinephrine support during cardiac surgery, Szekely, A., *et al.*, (*EACTA*) A 15
——, Doppler monitoring of diastolic left ventricular function does not increase the sensitivity of dobutamine stress echocardiography for detecting inducible demand ischaemia in anaesthetized patients, Seeberger, M. D., *et al.*, (*EACTA*) A.40
——, Echocardiographic and haemodynamic differences among patients undergoing the MAZE procedure, Bakola, A. A., *et al.*, (*EACTA*) A.44
——, Effect of dexamethasone on oedema formation in patients undergoing coronary bypass surgery, Giannaris, S , *et al.*, (*EACTA*) A.23
——, Effect of intravascular volume load after induction of anaesthesia on oxygen consumption in cardiac surgery patients, Ballesteros, M., *et al.*, (*EACTA*) A.19
——, Effect of temperature and cardiopulmonary bypass on the pharmacokinetics of remifentanil, Russell, D., *et al.* 456–459
——, Effects of antiotensin on renal function in cardiac surgical patients, Bennett, S. R., *et al*, (*EACTA*) A.18
——, Effects of chronic angiotensin converting enzyme inhibition on renal function during cardiac surgery: the role of atrionatriuretic factor and prostanoids, Schweizer, A., *et al.*, (*EACTA*) A.16
——, Effects of dexamethasone on release of endotoxin and cytokines during hypothermic cardiopulmonary bypass, Hóche, A., *et al.*, (*EACTA*) A.24
——, Effects of nicardipine on gastric mucosal perfusion during cardiopulmonary bypass, Lemoine, E., *et al.*, (*EACTA*) A 54
——, Effects of preoperative i.v. heparin in coronary artery bypass grafting, Collard, E., *et al.*, (*EACTA*) A.65
——, Effects of R97399, a new PDE III inhibitor in patients with ischaemic heart disease, Verborgh, C., *et al.*, (*EACTA*) A.10
——, Effects of temperature on phrenic nerve and diaphragmatic function during cardiac surgery, Mills, G. H., *et al.* 726–732
——, Effects of ventilation during cardiopulmonary bypass on pulmonary shunt, compliance and structure, Erhan, E., *et al.*, (*EACTA*) A.56
——, Efficacy of a vital capacity manœuvre to prevent post-cardiopulmonary bypass atelectasis: An experimental study, Magnusson, L., *et al.*, (*EACTA*) A 57
——, Evaluation of left ventricular function by load independent indicators, Jovic, M., *et al.*, (*EACTA*) A.35
——, Evaluation of the effects of diltiazem on myocardial protection with troponin T in coronary artery bypass graft surgery, Apkar, F Z., *et al.*, (*EACTA*) A.28
——, Gut mucosal perfusion in infants undergoing cardiopulmonary bypass: effect of preoperative captopril, Booker, P. D., *et al.* 14–18
——, Haemodynamic effects of celiprolol and sotalol after coronary artery bypass grafting, Foubert, L., *et al.*, (*EACTA*) A.90
——, Haemodynamic response to angiotensin in patients treated with angiotensin converting enzyme inhibitors, Bennett, S. R., *et al.*, (*EACTA*) A.13
——, Hepatic venous blood flow measured with retrograde thermodilution technique, Christiansen, C. L , *et al.*, (*EACTA*) A.55
——, Imipramine poisoning in an animal model-treatment with single cardiopulmonary bypass support or additional rein-haemoperfusion? Schmidt, W., *et al.*, (*EACTA*) A.64

——, Impact of preoperative pulmonary vascular resistance and ischaemic time on the cardiovascular function after orthotopic heart transplantation, Bertolissi, M., *et al.*, (*EACTA*) A.61
——, Improved intraoperative assessment of aortic stentless valves using transoeosophageal echocardiography, Morris, M. J., (*EACTA*).A.43
——, Influence of postoperative activated clotting time (ACT) on re-operations for bleeding after cardiac surgery, Szabo, Z., *et al.*, (*EACTA*) A 72
——, Influence of sevoflurane on cerebral metabolism, blood flow and CO_2-reactivity, Mielck, F., *et al.*, (*EACTA*) A.6
——, Influence of ventilation modes on analgesic and sedative demand and pulmonary gas exchange in patients after CABG-surgery, Kazmaier, S , *et al.*, (*EACTA*) A.88
——, Intravenous clonidine administration during CPB: effects on haemodynamic parameters and extubation time, Abay, G., *et al.*, (*EACTA*) A.8
——, Is severe obesity a risk factor for coronary surgery? Ranucci, M., *et al.*, (*EACTA*) A.84
——, Left ventricular remodelling (Batista procedure): early postoperative care, Vuk, Lj., *et al.*, (*EACTA*) A.96
——, Methaemoglobin (MetHb) production during nitric oxide (NO) inhalation, Aouifi, A., *et al.*, (*EACTA*) A 93
——, Normothermic perfusion: effects on postoperative multi-organ dysfunction, Ranucci, M., *et al.*, (*EACTA*) A.85
——, Perioperative transoesophageal echocardiography with low dose dobutamine: A feasible test for viability? Palmgren, I., *et al.*, (*EACTA*) A.41
——, Plasma antifibrinolytic activity after injections of two dosages of tranexamic acid, Isetta, C., *et al.*, (*EACTA*) A.69
——, Plasma bradykinin during cardiopulmonary bypass and the effect of angiotensin converting enzyme inhibition, MacLaren, A. J., *et al.*, (*EACTA*) A.17
——, Platelet effects of aprotinin and tranexamic acid, Ammar, T., *et al.*, (*EACTA*) A.68
——, Platelet-rich plasmapheresis reduces allogeneic platelet transfusions and cost in complex cardiac surgery, Price Stover, E., *et al.*, (*EACTA*) A.70
——, Postoperative morbidity after coronary artery bypass graft surgery without cardiopulmonary bypass, Collard, E., *et al.*, (*EACTA*) A.86
——, Postoperative myocardial ischaemia and changes in indices of myocardial oxygen balance in patients undergoing CABG surgery, Tupper-Carey, D. A., *et al.*, (*EACTA*) A.36
——, Predictors of atrial fibrillation in CABG surgery, Svedjeholm, R., *et al.*, (*EACTA*) A.83
——, Preoperative ACE inhibition and vasoconstrictor requirements post cardiopulmonary bypass, Manji, M., *et al.*, (*EACTA*) A.14
——, Quality control of carotid artery thrombendarterectomy by intraoperative transit time flow and resistance measurements, Walpoth, B. H., *et al.*, (*EACTA*) A.37
——, Rebound pulmonary vasoconstriction and desaturation on withdrawal of nitric oxide in infants after cardiac surgery, Knapik, P., *et al.*, (*EACTA*) A.94
——, Relations between the phosphodiesterase III inhibitors and cytokines in open heart surgery, Taç, T., *et al.*, (*EACTA*) A.25
——, Relationship between aortic cross clamp time and myocardial oxygen consumption during coronary artery bypass surgery (CABG), Langenberg, C. J. M., *et al.*, (*EACTA*) A 50
——, Significance of regional cerebral oxygen saturation (rSO_2) during open heart surgery, Papadimitriou, L., *et al* , (*EACTA*) A.51
——, The effects of remifentanil on systemic and cerebral haemodynamics in patients undergoing cardiac surgery, Scholz, J., *et al.*, (*EACTA*) A.7
——, The effects of sevoflurane on regional myocardial blood flow and metabolism, when used to control intraoperative hypertension in patients undergoing coronary artery bypass grafting, Kirno, K., *et al.*, (*EACTA*) A.5
——, Thrombin generation and protein C activation in cardiac surgery patients, Welters, I., *et al.*, (*EACTA*) A.22
——, Tramadol for post operative analgesia in coronary artery bypass graft surgery, Manji, M., *et al.*, (*EACTA*) A.87
——, Transoesophageal echocardiography in cardiac and vascular surgery: therapeutic implications and inter-observer differences, Schmidlin, D., *et al.*, (*EACTA*) A.38
——, Transoesophageal echocardiography of mitral and pulmonary venous flow as estimation of diastolic function, Pittarello, D., *et al.*, (*EACTA*) A.42
——, Transport and surgical ischaemic times· Can they have a different influence on the cardiovascular function after orthotopic heart transplantation? Bertolissi, M., *et al.*, (*EACTA*) A.60
Surgery, dental, Comparison of sevoflurane and halothane for outpatient dental anaesthesia in children, Paris, S. T., *et al.* 280–284
——, Pre-emptive analgesia using local anaesthesia: a study in bilaterally symmetrical surgery, Campbell, W. I., *et al.* 657–659
Surgery, endoscopy, Sevoflurane or halothane for paediatric endoscopy, Plowman, A., *et al.*, (*C*) 143–144
——, Thorascopic sympathectomy, Fredman, B., *et al.*, (*C*) 688
——, Thorascopic sympathectomy, Parry-Jones, A. J D., (*C*) 688
——, Thorascopic sympathectomy in the treatment of palmar hyperhidrosis: anaesthetic implications, Fredman, B., *et al.* 113–119
Surgery, gynaecological, Buscopan does not improve pain after laparoscopic sterilization, Wilson, C M., *et al.*, (*ARS*) 139–140P
——, Postoperative spirometry after laparoscopy for lower abdominal or upper abdominal surgical procedures, Joris, J., *et al.* 422–426
Surgery, laparoscopy, Anaesthesia for laparoscopic cholecystectomy in a patient with Eisenmenger's syndrome, Sammut, M. S., *et al.* 810–812
——, Pain after laparoscopy, Alexander, J. I. 369–378
——, Pigs are not human, Lentschener, C., *et al.*, (*C*) 691–692
——, Pigs are not humans, Bazin, J. E., *et al.*, (*C*) 691
——, Postoperative respiratory dysfunction: is the site of surgery crucial? McKeague, H., *et al.*, (*E*) 415–416
——, Postoperative spirometry after laparoscopy for lower abdominal or upper abdominal surgical procedures, Joris, J., *et al.* 422–426
Surgery, orthopaedic, Acute normovolaemic haemodilution decreases postoperative allogeneic blood transfusion after total knee replacement, Olsfanger, D., *et al.* 317–321
——, Autotransfusion in major orthopaedic surgery: experience with 1785 patients, Borghi, B., *et al.* 662–664
——, Comparison of extradural and general anaesthesia on the fibrinolytic response to total knee arthroplasty, Sharrock, N. E., *et al.* 29–34
——, Detection of arrhythmogenic cellular magnesium depletion in hip surgery patients, Zuccala, G., *et al.* 776–781
Surgery, otolaryngological, Comparison of perioperative ketoprofen 2.0 mg kg^{-1} with 0.5 mg kg^{-1} i.v. in small children during adenoidectomy, Nikanne, E., *et al.* 606–608
——, Granisetron reduces the incidence of nausea and vomiting after middle ear surgery, Fujii, Y., *et al.* 539–540
Surgery, paediatrics, Arterial switch for transposition of great arteries anaesthesia & postoperative care, Aouifi, A., *et al.*, (*EACTA*) A.91
——, Comparison of propofol and isoflurane ameliorating effects during rewarming period in paediatric cardiac surgery, Çamcý, E., *et al.*, (*EACTA*) A.58
——, The laryngeal mask for fibreoptic bronchoscopy in children, Mizikov, V., *et al.*, (*EACTA*) A.73
Surgery, spinal, Knee–chest *vs* horizontal side position during induction of spinal anaesthesia in patients undergoing lumbar disc surgery, Laakso, E., *et al.* 609–611
Surgery, thoracic, Accuracy and clinical performance of a continuous intra-arterial blood-gas monitoring system during thoracoscopic surgery, Zollinger, A., *et al.* 47–52
——, Anaesthesia for the surgery of emphysema, Conacher, I. D 530–538
——, Changes in regulators of the circulation in patients undergoing lung surgery, Boldt, J., *et al.* 733–739
——, Clonidine and neuroendocrine stress response during lung surgery, Novak-Janković, V., *et al.*, (*EACTA*) A.9
——, Continuous intra-arterial blood-gas monitoring, Graystone, S. J., (*C*) 815–816
——, Continuous intra-arterial blood-gas monitoring, Venkatesh, B., (*C*) 815
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——, Inhaled nitric oxide during anaesthesia for lung transplant, Della Rocca, G., *et al.*, (*EACTA*) A.77
——, Lung transplant oedema: Clinical characteristics and radiological assessment? Kellner, J., *et al.*, (*EACTA*) A.81
——, Perioperagive medical care of patients undergoing bilateral lung volume reduction for severe emphysema, Vassalli, F., *et al.*, (*EACTA*) A.79

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——, Thoracoscopic sympathectomy, FREDMAN, B., *et al.*, (*C*) 688

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Surgery, urological, Caudal tramadol for postoperative analgesia in paediatric hypospadias surgery, PROSSER, D. P., *et al.* 293–296

Surgery, vascular, Effect of felodipine on renal function and vasoactive hormones in infrarenal aortic surgery, DE LASSON, L., *et al.* 719–725

——, "Renal" dopamine, GIBBES, A R. J., *et al.*, (*C*) 263–264

——, "Renal" dopamine, INGLIS, A., *et al.*, (*C*) 263

Sympathetic nervous system, Changes in regulators of the circulation in patients undergoing lung surgery, BOLDT, J., *et al.* 733–739

——, Dissociation between the effect of nitrous oxide on spontaneous and reflexly evoked sympathetic activity in dogs, MA, D., *et al.* 525–529

Sympathetic nervous system, adrenergic block, Haemodynamic effects of celiprolol and sotalol after coronary artery bypass grafting, FOUBERT, L., *et al.*, (*EACTA*) A.90

ympathetic nervous system, catecholamines, Changes in regulators of the circulation in patients undergoing lung surgery, BOLDT, J., *et al* 733–739

—, Local anaesthetic agents inhibit $[^3H]$noradrenaline uptake into SH-SY5Y human neuroblastoma cells, JOYCE, P. I., *et al.*, (*ARS*) 677P

Sympathetic nervous system, clonidine, Does the addition of clonidine affect duration of analgesia of bupivacaine wound infiltration in inguinal hernia surgery? ELLIOTT, S., *et al.* 446–449

——, Intra-articular morphine and clonidine produce comparable analgesia but the combination is not more effective, GENTILI, M., *et al.* 660–661

Sympathetic nervous system, dopamine, Dopamine and intestinal mucosal tissue oxygenation in a porcine model of haemorrhage, GERMANN, R., *et al* 357–362

Sympathetic nervous system, dopexamine, No direct effects of dopexamine on the isolated perfused rat kidney, LEUWER, M., *et al.*, (*ARS*) 132P

——, Reperfusion after supracoeliac aortic cross-clamping in a rat model: Effects of dopexamine on mesenteric oxygen transport, lactate flux and jejunal luminal PCO_2, WU, X., *et al.*, (*EACTA*) A.49

ympathetic nervous system, noradrenaline, Effect of halothane on K^+ and carbachol stimulated noradrenaline release and increased $_i$ in SH-SY5Y human neuroblastoma cells, ATCHESON, R., *et al.* 78–83

Sympathetic nervous system, pharmacology, clonidine, Clonidine and neuroendocrine stress response during lung surgery, NOVAK-JANKOVIÈ, V., *et al* , (*EACTA*) A.9

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pathetic nervous system, phenylephrine, Extra-ulmonary effects of inhaled nitric oxide in swine with and thout phenylephrine, TRONCY, E., *et al* 631–640

thetic nervous system, sympathomimetic agents, erent influences of long-term ace inhibitor treatment orepinephrine support during cardiac surgery, ELY, A., *et al.*, (*EACTA*) A.15

perative ACE inhibition and vasoconstrictor ements post cardiopulmonary bypass, MANJI, M., *EACTA*) A.14

re, body, Heat retention using passive systems naesthesia · comparison of two plastic wraps, one ective properties, DEACOCK, S., *et al.* 766–769

e, effect, Effect of temperature and

cardiopulmonary b

remifentanil, RUSSE

——, Effects of temperat

diaphragmatic functi

G. H., *et al.* 726–732

Temperature, metaboli

febrile ICU patients, M

Temperature, monitorin

febrile ICU patients, M

——, Heat retention using pa

comparison of two plastic

properties, DEACOCK, S , e

——, Prevention of hypothermi

new electric blankets during ..os,

Y., *et al.* 796–797

Temperature, solubility, Effec ..ature on the solubility of desflurane, sevofl..ane, enflurane and halothane in blood, LOCKWOOD, G G., *et al.* 517–520

Textbook of Neuroanesthesia with Neurosurgical and Neuroscience Perspectives, ALBIN, M. S., (editor), (*R*) 412

The Pulmonary Artery Catheter in Critical Care—A Concise Handbook, PERRET, C , *et al.*, (*R*) 266

The Pulmonary Circulation: Moving From Passive to Active Control, PINSKY, M. R., *et al.*, (editors), (*R*) 266

Theories of anaesthetic action, Meyer–Overton, Effects of volatile anaesthetics on spontaneous action potential firing of cerebellar Purkinje cells *in vitro* do not follow the Meyer–Overton rule, ANTKOWIAK, B., *et al* 617–624

Theories of anaesthetic action, molecular, Effect of halothane on K^+ and carbachol stimulated noradrenaline release and increased $_i$ in SH-SY5Y human neuroblastoma cells, ATCHESON, R., *et al.* 78–83

Thrombopoiesis and Thrombopoietins: Molecular, Cellular, Preclinical and Clinical Biology, KUTER, D. J., *et al* , (editors), (*R*) 413

Toxicity, Methaemoglobin (MetHb) production during nitric oxide (NO) inhalation, AOUIFI, A., *et al.*, (*EACTA*) A.93

Transfusion, Platelet-rich plasmapheresis reduces allogeneic platelet transfusions and cost in complex cardiac surgery, PRICE STOVER, E., *et al.*, (*EACTA*) A.70

Transfusion, autotransfusion, Acute normovolaemic haemodilution decreases postoperative allogeneic blood transfusion after total knee replacement, OLSFANGER, D , *et al.* 317–321

——, Autotransfusion in major orthopaedic surgery: experience with 1785 patients, BORGHI, B., *et al.* 662–664

Ventilation, Effects of ventilation during cardiopulmonary bypass on pulmonary shunt, compliance and structure, ERHAN, E., *et al.*, (*EACTA*) A.56

——, Influence of ventilation modes on analgesic and sedative demand and pulmonary gas exchange in patients after CABG-surgery, KAZMAIER, S., *et al.*, (*EACTA*) A.88

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Ventilation, anaesthetics, effects of, Comparison between halothane and sevoflurane for adult vital capacity induction, HALL, J. E., *et al.* 285–288

Ventilation, frequency, Cardioventilatory coupling during anaesthesia, GALLETLY, D. C , *et al.* 35–40

Ventilation, hypoxic response, Effect of domperidone on the ventilatory response to transient hyperoxia in patients anaesthetized with isoflurane, FOO, I. T , *et al* 41–46

Ventilation, mechanical, Cuff deflation for easier weaning from ventilation, BAPAT, P , *et al.*, (*C*) 145

——, Cuff deflation for easier weaning from ventilation, SHNEERSON, J., (*C*) 145

——, Weaning: is the work of breathing via a tracheostomy tube similar to that via a tracheal tube? BAPAT, P. P , *et al.*, (*C*) 815

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Ventilation, one-lung, Accuracy and clinical performance of a continuous intra-arterial blood-gas monitoring system during thoracoscopic surgery, ZOLLINGER, A., *et al* 47–52

——, Changes in regulators of the circulation in patients undergoing lung surgery, BOLDT, J., *et al.* 733–739

——, Comparison of volume controlled with pressure controlled ventilation during one-lung anaesthesia, TUĞRUL, E., *et al.* 306–310

Ventilation, pattern, Artificial neural networks for distinguishing disturbed from undisturbed breathing, CALEB, P , *et al.*, (*ARS*) 682P

Ventilation, positive end-expiratory pressure, Laryngeal mask airway and uncuffed trachael tubes are equally

r closed system anaesthesia in
, D., *et al.* 289–292
re controlled, Comparison of volume
th pressure controlled ventilation during one-
thesia, TUĞRUL, E., *et al.* 306–310
, resuscitation, Management of the airway and
lation during resuscitation, GABBOTT, D. A., *et al.*
59–171
—, Management of the airway and ventilation during resuscitation, RICHARDSON, C., (*C*) 814
Ventilation, spontaneous, Effect of domperidone on the ventilatory response to transient hyperoxia in patients anaesthetized with isoflurane, FOO, I. T., *et al.* 41–46
Ventilation, volume controlled, Comparison of volume controlled with pressure controlled ventilation during one-lung anaesthesia, TUĞRUL, E., *et al.* 306–310
Vomiting, antiemetics, Granisetron reduces the incidence of nausea and vomiting after middle ear surgery, FUJII, Y., *et al.* 539–540
——, Ondansetron compared with metoclopramide in the treatment of established postoperative nausea and vomiting, DIEMUNSCH, P., *et al.* 322–326
Vomiting, incidence, Ondansetron compared with metoclopramide in the treatment of established postoperative nausea and vomiting, DIEMUNSCH, P., *et al.* 322–326
Vomiting, nausea, Granisetron reduces the incidence of nausea and vomiting after middle ear surgery, FUJII, Y., *et al.* 539–540
——, Ondansetron compared with metoclopramide in the treatment of established postoperative nausea and vomiting, DIEMUNSCH, P., *et al.* 322–326
Vomiting, nausea, surgical factors, Granisetron reduces the incidence of nausea and vomiting after middle ear surgery, FUJII, Y., *et al.* 539–540
——, Ondansetron compared with metoclopramide in the treatment of established postoperative nausea and vomiting, DIEMUNSCH, P., *et al.* 322–326